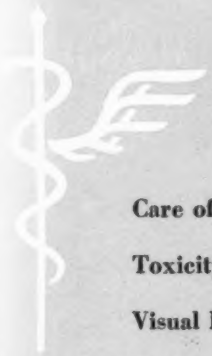
DOES NOT CIRCULATE

19[illegible] Assembly — Interstate Postgraduate Medical Association — Cleveland — November 10-13

Volume 24, Number 2 **AUGUST 1958**

Postgraduate Medicine



In This Issue

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Cases for Heart Surgery . . . **Henry Swan and S. Gilbert Blount, Jr.**

Scientific Exhibit (with color):
Chemopallidectomy and Chemothalamectomy . . . **Irving S. Cooper**

when eating moves outdoors . . .

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Clinical findings emphasize that COUMADIN is a drug that comes close to fulfilling the criteria of an ideal anticoagulant,[1-8] thus confirming the prediction of Link,[9] discoverer of Dicumarol[8]: COUMADIN *"will replace Dicumarol on the basis of its performance over a wide variety of conditions and... other anticoagulants will not be superior."*

speed of action – latent period 12-18 hours; about 97% of all patients show therapeutic hypoprothrombinemia in 24-48 hours, compared to 5 days for bishydroxycoumarin[3] – cuts need for initial heparin (when required) to day or less.[2,4,8,10]

sustained effect – initially induced therapeutic hypoprothrombinemia lasts up to 6 days, depending on dose;[10] oral maintenance dose of 5-10 mg. daily, according to individual need, assures steady level of safe but adequate anticoagulation.[2,8]

unsurpassed safety – based on smooth, stable prothrombin response and absence of cumulation; no toxic effects, low incidence of hemorrhage;[1,8] excessive hypoprothrombinemia is readily reversed by vitamin K_1 or menadione, often by discontinuation alone;[2,8,11] anticoagulant therapy can then be resumed without refractoriness.[2,3]

high predictability – initial dose almost invariably effective;[3] maintenance dosage readily and accurately estimated.[2,8]

low incidence of "escape" – 6-7% compared to 27% for bishydroxycoumarin.[3,8]

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TABLETS: *For oral use – 5 mg., peach, scored; 10 mg., white, scored; 25 mg., red, scored.*

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AVERAGE DOSE: *Initial,* 50-75 mg. (may be given with heparin[10]). *Maintenance,* 5-10 mg. daily, as indicated by prothrombin time determinations.

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References: *1. Goodman, D. H.: Arizona Med. 13:389, 1956. 2. Nicholson, J. H., and Leavitt, T., Jr.: New England J. Med. 255:491, 1956. 3. Nicholson, J. H.: Angiology 8:456, 1957. 4. Pollock, B. E.: J.A.M.A. 159:1094, 1955; 161:404, 1956. 5. Shapiro, S.: Surg. Clin. North America, Apr., 1956. 6. Kerrin, H. F., et al.: Angiology 8:302, 1957. 7. Brotman, I.: Am. J. Cardiol. 1:260, 1958. 8. Fremont, R. E., and Jagendorf, B.: J.A.M.A. 165:1941, 1957. 9. Link, K. P.: Paper presented at New York Acad. Med., Feb. 25, 1958, New York, N. Y. 10. Council on Pharmacy and Chemistry, A.M.A.: J.A.M.A. 159:1297, 1955. 11. Shapiro, S.: Angiology 8:498, 1955. 12. Olwin, J. H., and Koppel, J. L.: A.M.A. Arch. Int. Med. 100:842, 1957. 13. Clatanoff, D. V., and Meyer, O. O.: Ibid. 97:753, 1956. 14. Shapiro, S., and Ciferri, F. E.: J.A.M.A. 165:1377, 1957.*

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• OFFICE EQUIPMENT AND BASAL METABOLISM DETERMINATIONS

Q. Which types of electrocardiograph and basal metabolism machines are recommended for office use? Now that protein-bound iodine and radioiodine uptake tests are available, is there still clinical value in a basal metabolism test? How does it compare in accuracy with the iodine uptake tests?

M.D.—New York

A. The specific electrocardiograph appropriate to the needs of the individual physician will vary with circumstances and the character of his practice. The direct-writer machines popular in recent years have proved satisfactory in studying clinical problems. When it is desirable to have permanent records which will withstand abuse and provide a basis for excellent photographic reproductions, film-recording machines have certain advantages. The physician should choose an instrument for which service is readily available.

While opinions differ, the majority of physicians interested in thyroid disease continue to regard determination of the basal metabolic rate as an exceedingly useful test in clinical practice. The basal metabolism test measures an entirely different aspect of thyroid function than does the protein-bound iodine or radioiodine test. Prior ingestion of iodides, drugs containing iodine, mercurial diuretics or antithyroid drugs, as well as other common situations which may invalidate the protein-bound iodine or radioiodine test, do not affect the results of a basal metabolism test. Some physicians believe that the basal metabolic rate gives the most reliable measure of the severity of a thyroid disorder.

The intrinsic accuracy of the basal metabolic rate varies widely, depending on the method of testing and the administrative technic used. When carried out by open-circuit calorimetry, the test may be extraordinarily accurate; however, with the closed-circuit apparatus, which is commonly used, considerable variation in results is unavoidable. Such variation generally can be minimized by two or three repetitions of the test. If the basal metabolic rate is determined with maximal care and precision and if random variations are eliminated, it is more accurate than the test for protein-bound iodine and, perhaps, less accurate than the radioiodine test in determining the diagnosis of exophthalmic goiter. The basal metabolic rate possibly is of greater significance than the results of the other tests in diagnosing myxedema.

• ASCARIS LUMBRICOIDES

Q. In my practice in rural Puerto Rico, there is a high incidence of infestation with *Ascaris lumbricoides*. About a year ago, I started using a one dose treatment schedule for patients in whom *Ascaris* infections were evidenced by the passage of worms or the presence of ova in the stool. Initially, I used a 10 per cent solution of piperazine hexahydrate prepared from piperazine

(Continued on page A-20)

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for infants and children up to 4 years of age

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- lasts *twice* as long

Engran Baby Drops Contain:

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Vitamin A	2500 units
Vitamin D	500 units
Thiamine	0.6 mg.
Riboflavin	1.0 mg.
Nicotinamide	6.0 mg.
Vitamin C	35.0 mg.
Pyridoxine HCl	1.0 mg.
d-Panthenol	2.5 mg.
Vitamin B_{12}	3.0 mcg.

Supply: 15 cc. and 50 cc. bottles. Convenient 'Flexidose' dropper assures accurate dosage.

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citrate in doses of 20 cc. for patients weighing 10 to 40 lb., 30 cc. for patients weighing 41 to 65 lb., and 35 cc. for those weighing more than 66 lb. There were no apparent toxic manifestations and the cure rate, as shown by follow-up stool examinations, was over 90 per cent in 200 patients.

Because the cost was lower, I later used a 10 per cent solution of piperazine hexahydrate prepared from piperazine tartrate. In a series similar to the first, using the same technic and dosage schedule, the cure rate resulting from the use of this second preparation has dropped to practically nothing. I have had equally poor results using tablets of piperazine tartrate in the same or higher dosage.

Is there any explanation for this apparent difference in the effectiveness of piperazine hexahydrate prepared from the citrate and that prepared from the tartrate? Is there any reference to this comparison in the literature on the subject? Has the one dose method of treating *Ascaris* been endorsed or discussed extensively by public health authorities?

M.D.—Puerto Rico

A. Piperazine hexahydrate is not usually prepared in the chemical sense from its citrate or tartrate salts as implied in the inquiry. Ordinarily, piperazine is first synthesized as such and then is crystallized from aqueous solution as the hexahydrate. In this form it is a strong base which readily absorbs carbon dioxide from the atmosphere and undergoes changes on exposure to light.

From this base, salts are prepared for use in pharmaceuticals. The common forms are the citrate (ANTEPAR® citrate and PIPIZAN® citrate), tartrate (PIPERAT®) and phosphate (PIPERAZATE® wafers). In each case the activity of the drug is ascribed to the base, piperazine hexahydrate. The anions are inert and serve to improve factors of stability for formulation. So far as is known, these salts are equally active when given in doses representing equivalent amounts of the base.

Pharmaceuticals containing the citrate or the tartrate are commonly labeled to indicate their potency in terms of equivalent amounts of piperazine hexahydrate. This eliminates the need for calculating piperazine content to compensate for differing molecular weights when doses of the different preparations are being compared. Syrups presently available contain citrate or tartrate salts equivalent to 100 mg. of piperazine hexahydrate per cubic centimeter; these conform to the 10 per cent solutions described in the inquiry. It seems unlikely that the inquirer actually carried out the chemical conversions; it is to be noted that he also had poor results from the tartrate in tablet form.

The foregoing comments offer no explanation for the poor results obtained in using tartrate preparations unless, of course, some chemical procedures were carried out. Possibly, chemical deterioration occurred during storage.

The manufacturers of Pipizan citrate and Piperazate wafers (piperazine phosphate) describe a one day course of treatment for ascariasis in which doses are used approximating those employed by the inquirer. These companies may be able to supply comparative evaluations of the several treatment periods.

• CALCIFICATION OF COSTAL CARTILAGES

Q. Is there any clinical significance attached to the finding of marked calcification of the costal cartilages in young people? I have seen this before, and it has been explained to me as a phenomenon not necessarily abnormal. For about six months, a 32 year old patient has been complaining of pain in the anterolateral region of the left lower ribs. The chest x-ray reveals marked calcification of all the costal cartilages; rib x-rays reveal no abnormality. Hemoglobin, white blood count, sedimentation rate and urinalysis are all normal. Serum calcium is 12 mg. per cent, and urinary calcium (Sulkowitch) is in the normal range. No symptoms of renal disease are present. Can the findings of rib pain and tenderness be associated with marked calcium deposition, and if so what is the underlying cause?

M.D.—Arkansas

A. Painful, calcified costal cartilages are not unusual findings. However, there seems to be no connection between the calcification and the pain, since they frequently occur separately. Calcification of the costal cartilages progresses with age; it rarely is seen in patients less than 20 years of age, but it is not an infrequent finding on routine chest x-rays in patients more than 40. Although the location of the painful cartilage in the case given is not typical, the presence of Tietze's syndrome (painful, nonsuppurative swelling of costal cartilages) cannot be excluded. As to treatment, heat and local injection of hydrocortisone should be tried.

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tablets

Composition

METICORTEN® (prednisone)	0.75 mg.
Acetylsalicylic acid	325 mg.
Aluminum hydroxide	75 mg.
Ascorbic acid	20 mg.

Packaging: SIGMAGEN Tablets, bottles of 100 and 1000.

References: 1. Spies, T. D., et al.: J.A.M.A. 159:645, 1955. 2. Spies, T. D., et al.: Postgrad. Med. 17:1, 1955. 3. Gelli, G., and Della Santa, L.: Minerva Pediat. 7:1456, 1955. 4. Guerra, F.: Fed. Proc. 12:326, 1953. 5. Busse, E. A.: Clin. Med. 2:1105, 1955. 6. Sticker, R. B.: Panel Discussion, Ohio State M. J. 52:1037, 1956.

Acute conditions: Two or three tablets four times daily. After desired response is obtained, gradually reduce daily dosage and then discontinue.

Subacute or chronic conditions: Initially as above. When satisfactory control is obtained, gradually reduce the daily dosage to minimum effective maintenance level. For best results administer after meals and at bedtime.

Precautions: Because SIGMAGEN contains prednisone, the same precautions and contraindications observed with this steroid apply also to the use of SIGMAGEN.

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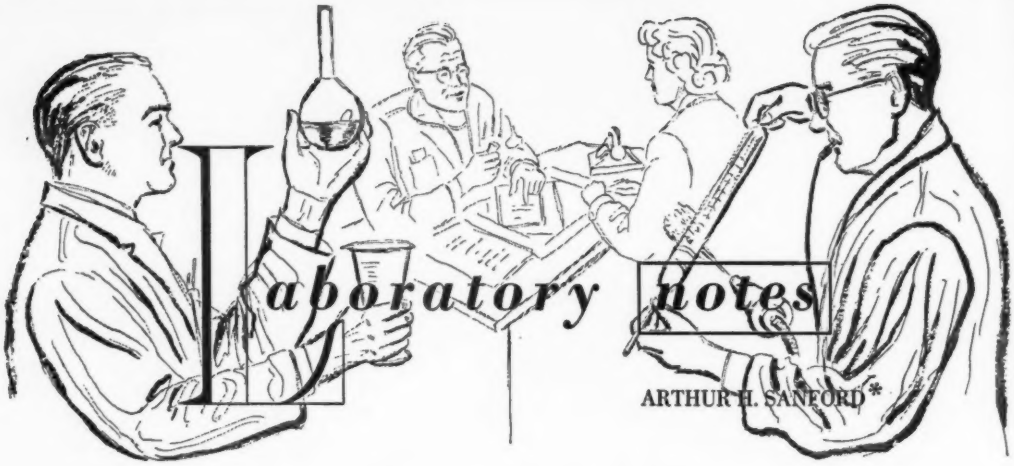


ARTHUR H. SANFORD*

Infectious Hepatitis

RECENTLY the following query from a physician in Maine was sent to POSTGRADUATE MEDICINE and referred to me for reply:

"By regulation of the Department of Health and Welfare of Maine, all patients in that state who have infectious hepatitis are placed in complete isolation for the first 10 days.

"In my fairly recent hospital training, there was no isolation of such patients, although, of course, precautions were taken regarding instruments contaminated with blood or blood products and excreta.

"It is my impression that living virus is present in stool and urine for at least six months and that transmission is believed to occur through contamination with either blood or excreta. Consequently, such an arbitrary isolation period seems, at the least, unreasonable.

"I would appreciate your comments and some references to sources of information."

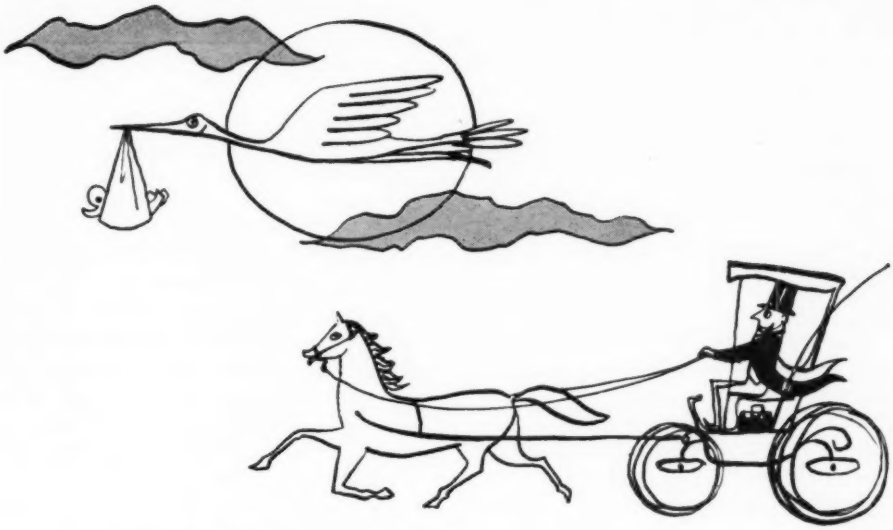
In the official report for 1955 of the American Public Health Association on the "Control of Communicable Diseases in Man," infectious hepatitis is identified as an acute infection with vague prodromal symptoms of fever, anorexia, nausea, fatigue, headache and abdominal discomfort. Leukopenia is usually present. After a few days the fever subsides, and the patient becomes jaundiced. This second phase is of variable duration, and it may be very mild or may be so severe as to cause acute yellow atrophy and death. The disease is also known as catarrhal jaundice, epidemic hepatitis or epidemic jaundice; it is believed to be caused by a virus. The incubation period varies from 10 to 40 days. The mode of transmission is not known, but it is believed that the greatest danger of communicability is in the first phase of the disease. The recommendation of the American Public Health Association is to report the disease to the local health authority and to isolate the patient during the first week of the illness.

Because of the ruling in the state of Maine, I have tried to learn the regulations in other states. Letters were sent to 48 state health departments and to the District of Columbia.

The code is being revised in the District of Columbia, and the recommendation will be to isolate patients who have this disease for one week. There are four states in which the health officer believes that it is not advisable to recommend isolation because of the variability in the symptoms and difficulty of diagnosis during the first week of illness. However, nearly all states now have the recommendation or regulation that the patient be isolated for one week or as long as he is febrile. Since 1954 the regulation in Iowa has been to "increase the period of one week's isolation of the case to cover the period of clinical illness." In Michigan and North Carolina, the regulation is practically the same.

(Continued on page A-28)

*Emeritus Staff, Section of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.



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In 1954 the Oregon State Board of Health published an attractive six page booklet on infectious hepatitis which described the disease, the manner of transmission, symptoms and treatment and contained good diet lists. It also stated that since 1948 reported hepatitis had increased 500 per cent in that state. It is apparent that the disease should be reported and the patient should be isolated, if possible.

In the state of Washington, the regulations require isolation of patients only in institutional outbreaks. Following the recommendation of the American Public Health Association, it is suggested that the isolation period be for seven days after onset.

Table 1 shows the reported cases of infectious hepatitis in Minnesota, covering five year periods from 1934 to 1953.

TABLE 1

REPORTED CASES OF INFECTIOUS HEPATITIS IN MINNESOTA

YEARS	NUMBER OF CASES	DEATHS
1934 to 1938	72	6
1939 to 1943	380	5
1944 to 1948	610	33
1949 to 1953	2,071	45

New rules governing reportable diseases became effective July 1, 1958. Infectious hepatitis: "(1) Whenever the health officer shall know of or suspect a case or group of cases of infectious hepatitis he shall conduct an investigation of all the circumstances and prescribe such quarantine or isolation procedures for patients or contacts as shall best be calculated to prevent spread of the disease to others. (2) The health officer shall require concurrent disinfection of feces and vomitus of patients and articles soiled therewith and shall prescribe methods for disposal of human wastes consistent with the sanitary regulations of the Mississippi State Board of Health."

The young physician in Maine raised a question which proved to be quite enlightening when I attempted to answer it in the light of present knowledge. Perhaps some of the readers of this column may wish to comment on this subject from personal experience.

MEETINGS and Postgraduate Courses

AMERICAN ACADEMY OF PEDIATRICS, CHICAGO: Annual meeting, October 17-23, at the Palmer House. Program will include seminars, October 18 and 19, and round tables and general sessions, October 20-23. For further information, write to: Executive Office, American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, Illinois.

AMERICAN UROLOGICAL ASSOCIATION ANNUAL AWARD CONTEST: An award of $1000 (first prize $500, second prize $300, and third prize $200) is offered for essays on the result of clinical or laboratory research in urology. Competition is limited to urologists who have been graduated not more than 10 years, and to hospital interns and residents doing research work in urology. The first-prize essay will be presented before the American Urological Association meeting at the Chalfonte-Haddon Hall, Atlantic City, April 20-23, 1959. Entries must be received by December 1, 1958. For further information, write to: William P. Didusch, Executive Secretary, 1120 North Charles Street, Baltimore 1.

ENDOCRINE SOCIETY, SYRACUSE: The tenth postgraduate assembly in endocrinology and metabolism, in the auditorium of the College of Medicine, State University Upstate Medical Center, September 29-October 3. For further information, write to: Dr. William A. Harris, Dean of Postgraduate Education, State University Upstate Medical Center, 766 Irving Avenue, Syracuse 10.

STATE UNIVERSITY OF IOWA COLLEGE OF MEDICINE, IOWA CITY: Postgraduate courses for 1958-1959.

Pediatrics, September 17-18
Iowa Urological Society, September 26-27
Anesthesia for the part-time anesthetist, October 9
Iowa Radiological Society, October 10-11
Clinical physical medicine and athletic injuries, November 21-22
General surgery, December 9-11
Obstetrics and gynecology, January 14
Refresher course for the general physician, February 17-20
Neurology conference, March 19
Cardiac auscultation, April 8-9
Alumni day, June 12-13

For further information, write to: Dr. W. C. Keettel, Director, Postgraduate Medical Studies, College of Medicine, Iowa City.

THIRD INTERNATIONAL CONGRESS OF ALLERGOLOGY, PARIS: October 19-26. Sponsored by the International Association of Allergology and French Allergy Association. For further information, write to Dr. B. N. Halpern, 197 Boulevard St. Germain, Paris 7.

What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

BOTTLE FEEDING ON INCREASE

American Medical Association:

- In a survey of 1,904 hospitals, data showed 63 per cent of infants are bottle-fed, 21 per cent breast-fed, and 16 per cent fed from both breast and bottle. A similar study in 1946 showed 36 per cent, 37 per cent and 27 per cent, respectively. Eighty-four per cent of mothers and infants leave the hospital on or before the fifth postnatal day, just when the maternal lactation is being established.—Dr. Herman F. Meyer, Northwestern University Medical School, Chicago.
- Exfoliative cytology is 95 per cent accurate in diagnosing cancer of the esophagus, colon and stomach and 60 per cent accurate in diagnosing cancer of the pancreas and biliary duct. X-ray should be used for screening, and cytologic study for more precise information.—Dr. Howard F. Raskin, University of Chicago School of Medicine, Chicago.
- DBI, one of a group of drugs known as biguaneides, has lowered the blood sugar level in 107 of 173 patients treated at Joslin Clinic. Forty-three other patients could not tolerate the drug and 23 could not be helped. Thus about two-thirds responded to the drug as compared with 70 per cent of adults who responded to tolbutamide. The patients receiving DBI were unselected and included juveniles.—Dr. Leo P. Krall, Boston.

CORTISONE FOR AMENORRHEA

Endocrine Society:

- Physiologic doses of cortisone or hydrocortisone produced resumption of regular ovulatory cycles in 34 of 39 patients with amenorrhea or irregular ovulatory cycles. Improvement was seen as early as one month after therapy, but the average was three months. Sixteen of 27 infertile women in the group became pregnant. Mild adrenal disorders thus may be the cause of ovarian dysfunction.—Drs. W. McK. Jeffries and R. P. Levy, Western Reserve University, Cleveland.
- Growth was stimulated in three patients with panhypopituitarism who received growth hormone. The patients, aged 13, 14 and 27, received 0.1 to 5.0 mg. of the hormone intramuscularly daily for 30 to 57 days during complete balance studies. Pattern of response suggested stimulation of fat catabolism, which may represent a primary site of growth hormone action.—Dr. Philip H. Henneman, Massachusetts General Hospital, Boston.

New steroid for arthritis

American Rheumatism Association:

• A new synthetic steroid, 25 times more potent than hydrocortisone and six times more potent than prednisone, may have greater anti-inflammatory activity than any corticosteroid yet produced. In a series of 18 patients, nine had increased sweating, insomnia and transitory skin spots. There were no major side effects, such as high blood pressure, activation of peptic ulcers, and edema. The drug, known as hexadecadrol, will not be available for general use for some time. Whether side effects will appear after prolonged administration remains unanswered.—Dr. Joseph J. Bunim, National Institute of Arthritis and Metabolic Diseases, Bethesda.

• The usefulness of aspirin in arthritis may be due in part to hyperventilation produced by heavy doses. In five of nine patients tested, sedimentation rates decreased following hyperventilation artificially produced with a Drinker respirator.—Dr. Frederick Kahn, Los Angeles.

Unsuspected hypothyroidism cited

American Therapeutic Society:

• A large-scale survey among 4500 men in industry in southern California showed that 7 per cent had thyroid deficiency. Projecting these findings, it may be estimated that one million working men in the United States have hypothyroidism, unbeknown to them or their physicians. The technic of determining protein-bound iodine (PBI) is an excellent screening device.—Dr. Paul Starr, University of Southern California School of Medicine, Los Angeles.

• Addition of mephenesin speeds salicylates to the site of arthritic pain. It results in more rapid appearance of salicylate in the blood stream than occurs when aspirin or sodium salicylate alone is given.—Dr. Robert Batterman, New York Medical College-Flower and Fifth Avenue Hospitals, New York.

Radioiodine-induced nodules

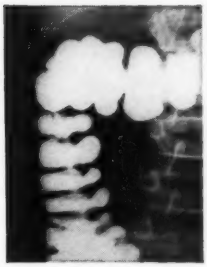
American Goiter Association:

• Thyroid nodules may result from radioiodine therapy for hyperthyroidism in children. In a group of 213 patients with toxic diffuse goiter treated over a 10 year period with I^{131}, five were children less than 10 years old. In two of them, nodules developed 8 and 10 years, respectively, after treatment. Palpable nodules also developed in 1 of 13 patients who were between ages 10 and 20. Among 195 patients more than 20 years old, nodules developed in two of them 12 and 15 months after treatment, but it is possible these were present before therapy and were disclosed by shrinkage of the tissues induced by radiation.—Drs. Glenn E. Sheline and Stuart Lindsay, University of California School of Medicine, San Francisco.

Heart surgery broadened

Society for Vascular Surgery:

• With artificial heart-lung machines becoming the method of choice for open-heart surgery, conservative, nonoperative treatment of many types of heart defects can no longer be justified. Mortality is less than 5 per cent for certain operations. Hypothermia may finally be employed only as an aid in the repair of certain valvular defects and as a metabolic adjunct in a variety of surgical procedures. An adequate supply of blood is one of the present bottlenecks of artificial heart-lung surgery. An average operation requires 8 pt. heparinized blood and an additional 5 pt. for use in the postoperative period.—Dr. Frank Gerbode, Stanford University School of Medicine, San Francisco.



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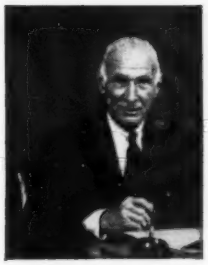

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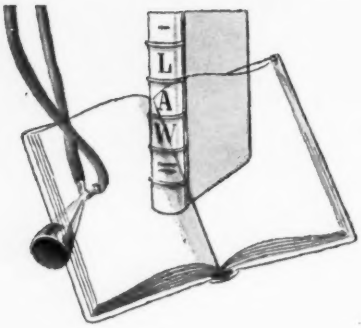

Forensic Medicine

Responsibilities of Owning and Using X-ray Equipment

ROGER A. HARVEY*

University of Illinois College of Medicine, Chicago

ROGER A. HARVEY

I AM hesitant to add more discussion to the present clamor over the damage caused by radiation, but I am becoming more convinced that in trying to calm patients' fears the health professions are overlooking many of their own responsibilities. The basic situation is medical, but we are apparently letting legislative action and liability insurance reappraisals take the initiative to such a degree that our methods of practice will be restricted before we realize what has happened. The present discussion is intended to cover some of the background of the development of lay attitude, the measures to be taken by all users of radiation-emitting machines or sources in order to prevent further restrictive legislation or liability coverage, and some of our responsibilities to those lay workers in the radiation areas.

The existence of radiation hazards is not a new finding. Almost since the discovery and early use of x-rays and radium, awareness of their dangers has gradually increased. By inference, study and dramatization of radiation effects from modern weapons have made all uses of radiant energy appear unduly risky. It is easy to see how laymen have accepted this viewpoint when one realizes that the use of x-rays has been associated chiefly with such personal disasters as war and disease. As a result, we are in an era when we can expect radiation to be blamed for almost any damaging effect; therefore, we should exercise caution in its use and employ precise knowledge of how much, if any, harm each examination can cause. The argument that the ultimate good to the patient outweighs the risk of exposure to x-rays to this or subsequent generations will require greater specificity.

Other than specialists in radiology, few physicians have much appreciation of the great strides which have been made by manufacturers of x-ray equipment and accessories in cooperation with radiologists and of the progress made by the latter group in practicing greater protection from radiation for their patients and themselves. These improvements have not been effected overnight as a result of the radiation scare; they have been steadily increasing for decades. Unless there is widespread recognition of these advances from

(Continued on page A-38)

*Department of Radiology, University of Illinois College of Medicine, Chicago, Illinois.

in each of these indications for a tranquilizer...

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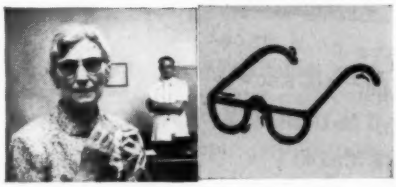

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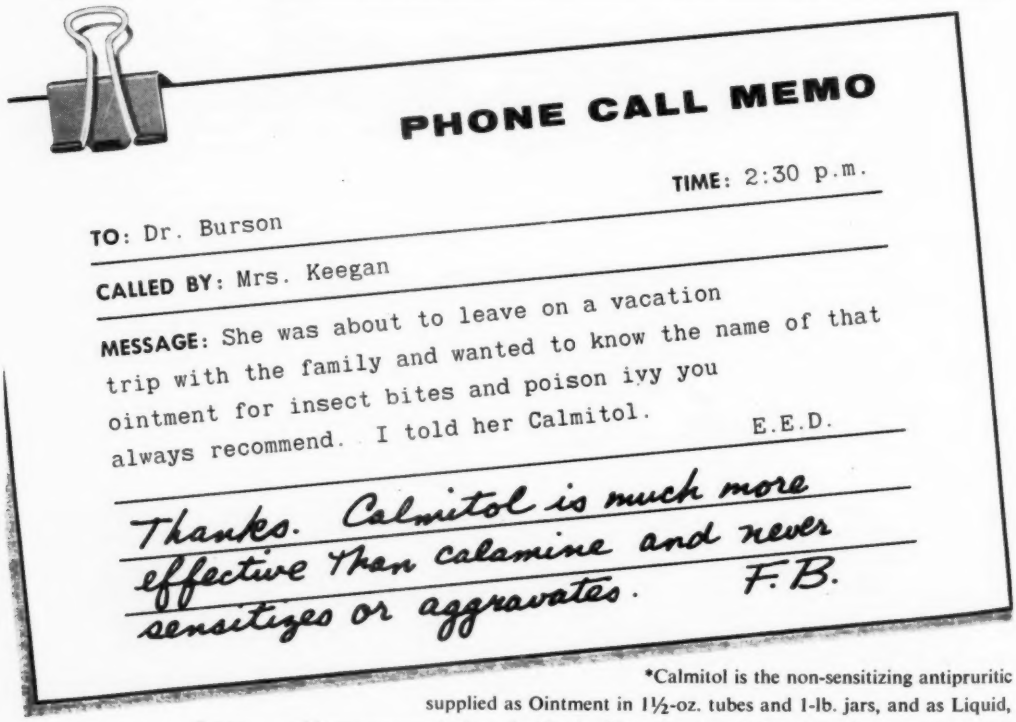
within the general medical profession, evidenced by the abandonment of obsolete equipment and revision of individual methods of use, increasing numbers of persons who use radiation equipment will be subject to future liability claims of fantastic proportions. Many states already have enacted legislation which varies from registration to absolute restriction of practice, if the laws are fully enforced as written. Many larger cities have or are in the process of setting up codes which range from banning use of radiation in certain conditions (through prohibiting use of obsolete equipment) to actual licensing of users. How far this type of activity will go is not known, but it certainly is making the public conscious of personal liability. The only way to slow this trend is for each user to have proof that he is using safe equipment, that he is familiar with its radiation output, and that he minimizes unnecessary exposure to his patients and himself.

Why is so much emphasis placed on hazards of medical radiation exposure? Our increased environmental contamination from weapons testing is here to stay for a long time, and medical and industrial sources of radiation are the only ones which can be turned on and off at will. Therefore, they are the only ones which can be reduced significantly. In medicine we are primarily exposing people, while in industry we are primarily exposing materials, although it is possible that people working near the materials may receive some degree of exposure. A more important reason for emphasizing radiation hazards is a changing attitude toward the threshold dose for effect from radiation. As methods are devised for measuring the effects of smaller and smaller radiation doses, it is becoming apparent that the threshold level may well be below the least possible level which we currently can measure and detect. Some of the newest textbooks completely miss the point of this changing concept as well as the basic laws of genetics, by stating that a given x-ray procedure is safe inasmuch as no one has ever proved that any harm results from it. The harm will not be recognized in human subjects by this generation or possibly several more, but when

(Continued on page A-40)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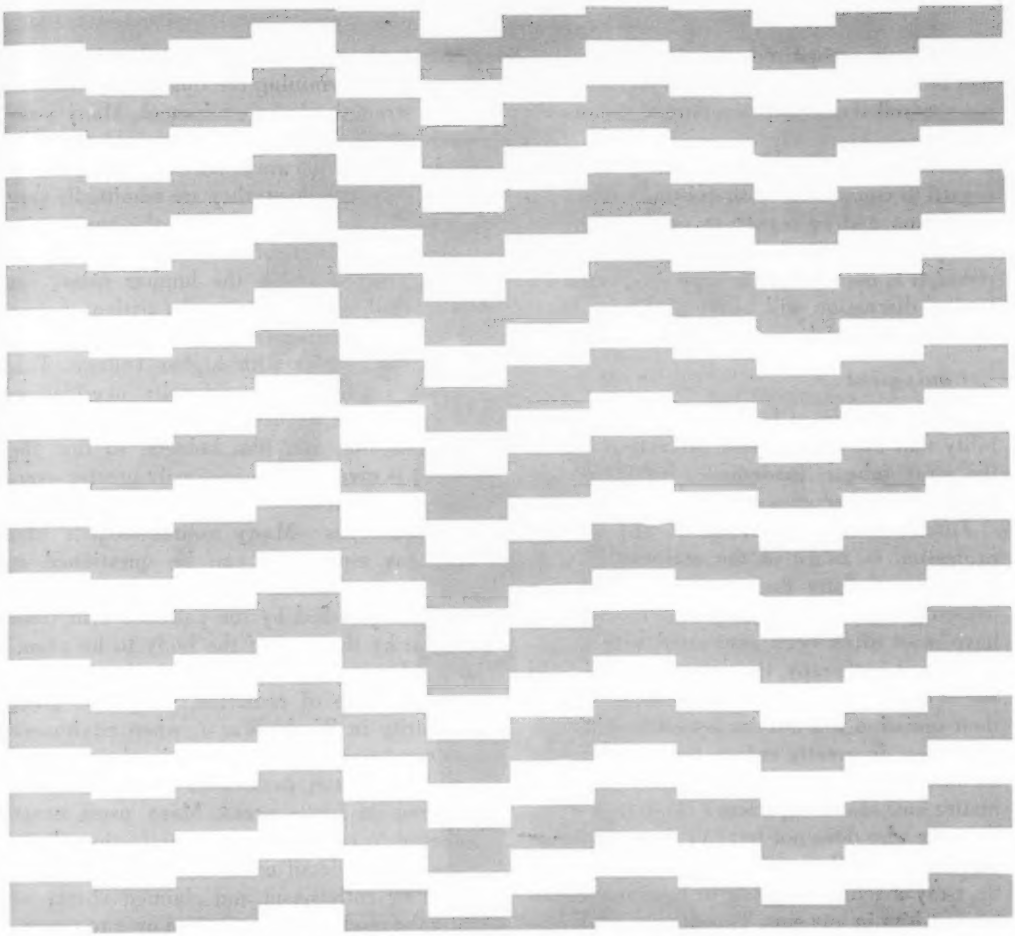

rational adjunct to tranquilizing therapy

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1. Campbell, D. G.: In: *Modern Nutrition in Health and Disease*, Wohl, G. M. and Goodhart, R. S. (Editors), Lea & Febiger, Philadelphia, 1955, p. 814.

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and if it is recognized, the genetic patterns will be too diffused in the entire population to use controlled selective breeding to remove the defects.

How can we evaluate our own situation in regard to compliance with existing or possible legislation and in regard to conformity with safe practice from the standpoint of liability risks? It is hoped that the divisions in the following discussion will be helpful as a check list in making such an evaluation.

Equipment

As the equipment becomes older the possibility that the built-in lead protection around the x-ray tube is inadequate, leaking or entirely lacking becomes greater.

Filters—Nearly everyone in the medical profession is aware of the malpractice suits based on a claim that omission of a filter caused severe tissue damage. Although filters have most often been associated with equipment used in therapy, they also are considered essential on diagnostic x-ray machines. While their omission will not cause visible skin reaction, they do greatly reduce the possibility of an unnecessary radiation dose to a patient. No matter how absurd a patient's claim may seem, the user who does not have or does not know whether or not there are filters on his diagnostic x-ray machine is going to have one strike against him in any suit. This applies to fluoroscopes as well as to radiographic machines; 2 mm. of aluminum is now recommended as the minimum thickness for filters. If it is possible to see the filament glow in the x-ray tube from the patient's position, there is no added filter and one should be obtained.

Cones—It is difficult to imagine a situation which would not require some type of lead diaphragm or cone on the x-ray machine, as this device limits the spread of the x-ray beam. The smallest-sized cone consistent with coverage of the area to be studied is recommended. None of the standard sizes of x-ray film are large enough to include the whole field of coverage from a tube without a diaphragm or cone. In other words, why expose more of the patient than is to be recorded on the film or observed in the fluoroscopic screen?

Strength of equipment—Another important factor in determining the dosage of radiation is the strength of the equipment. Many x-ray machines have been built and sold for relatively light x-ray work, such as that pertaining to the extremities; they are admittedly very reasonable in price. Too often the owner tries to extend the use of that same machine to heavy areas, such as the lumbar spine, not realizing that he is giving the patient a dose of x-ray unnecessarily greater than that delivered by a unit with higher voltage. This hazard, caused by occasionally overloading the equipment, is usually increased by inappropriate film and film holders, so that the patient is given an unnecessarily greater overdose of radiation.

Fluoroscopes—Many nonradiologists who use x-ray equipment can be questioned at times as to whether or not the use of fluoroscopy is justified by the patient's symptoms or even by the part of the body to be examined. Fluoroscopy is without doubt the most abused source of radiation. It gained great popularity in World War I, when equipment was cumbersome, films were in the form of glass plates, and darkrooms presented great problems in battle areas. Many users never bothered to compare subsequently the advantages of film detail over fluoroscopic images, and their enthusiasm and claimed ability of using the modality have carried over to younger physicians. The trouble is that few users really limit the fluoroscope to observing physiologic function or motion and detecting certain types of opaque foreign bodies; still fewer have had really appropriate training in the use of a fluoroscope. Furthermore, the fluoroscope generally allows only one man an impression of what he thought he saw; it makes no record for future study and comparison, even though it *delivers far more radiation dose* to a patient than does a film examination. It is becoming increasingly important to measure the radiation output of every fluoroscope in terms of roentgens per minute, and an exposure interval clock should be present in the circuit so that one can make a note of the actual duration of fluoroscopic exposure to

(Continued on page A-42)

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the patient. If these recordings are long and high, it is obvious that the user should change his methods in order not to be self-incriminating in case of legal action.

Premises

X-ray equipment is being used in many offices and homes without adequate structural features to give complete protection from stray irradiation to the user and, in some instances, to his neighbors and family. Eventually, inspections will be enforced by laws or codes, and those who use such equipment without adequate shielding will be forced to discontinue use of the apparatus or install expensive additional protective features. Either event will raise questions and very likely lead to some claimed injuries to neighbors or even long-time, loyal employees. Surveys of the adequacy of present protection should be made at once, and if there is any question about where to obtain such specialized help, the equipment or film supplier can easily provide the information. In some situations new and more powerful equipment has replaced older units, and there are good possibilities that structural protection features may not have been correspondingly increased. This could cause a previously safe position to become hazardous.

Personnel

No one has any special protection from the effects of irradiation, although some people occasionally seem to think that radiologists and their trained technicians have special immunity as a result of special training. In some instances, even this special knowledge and familiarity can lead to disastrous carelessness, just because nothing has happened yet or because one has lived beyond his expected years of needed reproductivity.

Good practice requires (1) the least possible exposure to afford optimum diagnostic aid, (2) the continual awareness that doubling the distance between x-ray sources and employee or self reduces personal exposure to one-fourth that at the closer position, and (3) that there be available and in evidence good lead gloves, lead aprons, sheets of leaded rubber and various-shaped cutouts to apply to patients to protect areas not necessary to be visualized by the rays.

Personnel- and self-monitoring is strongly recommended on a continuing basis if x-rays are taken or fluoroscopic studies are made several times a week. This can be done conveniently by the use of film badges, which can be obtained from several nationwide distributing sources; they are advertised in several journals and are known to all suppliers of x-ray equipment and film. We have used them for several years and have noted a yearly decline in the total irradiation dosage picked up by the combined personnel of the department. Any person showing an overexposure for any week has to account for it in writing by explaining what happened and what steps have been taken to prevent recurrence. Employment policies give us the power to suspend or transfer a chronic offender to much less desirable work for a penalty period. We discovered one potential troublemaker by becoming suspicious of the fact that his exposure record showed identical doses week after week even though his duties varied. When presented with the evidence and our theoretical explanation, he reluctantly admitted that he had been intentionally placing his badge in an x-ray beam, unfortunately for his purposes, for the same time interval each week. For protection, a neighboring institution which had another chronic offender temporarily engaged a qualified radiation physicist who showed that when the daily work was done according to the rules of the department no overexposure occurred. That employee has realized that her employer is not going to take the responsibility for her carelessness, and her self-exposure has remained well within safe limits since then.

Blood counts are no longer considered adequate indicators of personal radiation exposure. The counts are relatively insensitive to small amounts of exposure, and the effect is delayed too long to make an accurate correlation between causative episode and effect. We do obtain pre-employment blood counts and differential counts on all new technician employees, and, as a matter of added protection, do a final count when they terminate employ-

(Continued on page A-44)

When **tension, anxiety** accompany a clinical picture of overweight

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ment. Interim blood counts are available to them and still appeal to the older technicians, but they are not necessary in view of our constant use of film badges, which are so much more sensitive and reliable. We would, however, use blood counts in an accident situation where a large overexposure had been recorded on film badges.

The nursing service here has developed a plan whereby we utilize a crew of relatively older nurses' aides and orderlies to provide an x-ray patient-watching and patient-holding service. When an infant or unreliable elderly patient has to be constantly attended in the department or when special holding is necessary during filming, these people are used. Of course they are provided with leaded aprons and gloves and they all wear film badges, so that overexposure is guarded against even at a relatively advanced age. This gives us an experienced group of patient attendants and relieves young parents and, especially, young aides and student nurses from a potentially hazardous, recurring situation.

Terminology

Anyone who uses radiation equipment or renders reports on patients who have been treated or otherwise exposed to radiation should exercise increasing care in his choice of words describing or diagnosing or in any way implicating a situation. There is a fairly general impression that the term "x-ray burn" signifies something less than desirable, and it is quite often the grounds for a malpractice suit. Too many nonradiologists continue to use the term to describe any visible effect of radiation on skin, even though it may be transient, necessary and expected. Many patients go to a lawyer and on to "grievous anguish and suffering" at the mere sound of the term.

Not long ago I was asked to see a patient from another institution who claimed to have had diminished visual acuity in one eye, following x-ray treatment of an epithelioma of the eyelid. There was the old, recurring claim that a protective lead eyeshield had not been used. While there were some minor corneal changes present behind the treated area of the eyelid, the situation was made to appear ridiculous in court when the record showed that a reputable ophthalmologist who had seen the patient during his worst symptomatic stage had entered a diagnosis of "radioactive keratitis" in the patient's chart! Very likely he meant "radiation keratitis," and, of course, it was easy to prove that no radioactive substance had been used in this case.

Industrial Precautions

Industrial plant physicians have additional responsibilities in this field, and in some situations there is need for clarification of responsibility between the safety engineers and the physician. Outside the medical department itself, there may be additional potential hazards from radiation sources used to inspect, gauge and grade industrial products or processes. Usually, the employees involved in a process are trained to work under safe conditions, but I have seen several examples of remodeling or realignment of functions which place employees working nearby in jeopardy. Still greater hazards result from the storage of temporarily or permanently unused radiation sources, their danger being gradually forgotten as retirements and layoffs change the familiarity factor of the working crew. The changing levels in permissible dose exposure should be recognized, and reinspections should be made to be sure that continuing procedures are still safe in light of newest recommendations.

Union representatives are often familiar with hazardous situations in a general way; in my local experience they have often opposed or delayed the performance of duties by maintenance employees, even though extreme precautions were being used for the relatively slight chance of insignificant exposure. The work involved such tasks as wall painting and plumbing in a remodeling of areas adjacent to radiation installations. The fact that the work area had been evaluated and declared safe by radiation health physicists made no impression, probably in relation to possible reclassification of workers for the work area.

However, it is important that the medical profession retain the ultimate role in decisions in this area. Otherwise, there is the possibility

(Continued on page A-47)

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1. Shalowitz, M.: Geriatrics 11:312, 1956. 2. Warter, P. J.: J. M. Soc. New Jersey 54:7, 1957. 3. Hutcheon, D. E., et al.: Paper presented at Am. Soc. Pharmacol. & Exper. Therap., Nov. 8-10, 1956, French Lick, Ind. 4. Strub, I. H.: To be published. 5. Individual Case Reports to Medical Dept., Pfizer Laboratories.

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that entire departments or industries will be given special hazard-pay classifications simply because a radiation source is used somewhere in an inspection process or to generate power in a large industrial or utility plant.

Of greater importance is the need for continued vigilance, so that employees who are not oriented to radiation hazards are somehow prevented from doing absurd things carelessly. I have found painters who were scheduled for only one or two hours of work for one day in a room next to a radiation source, eating their lunch in the room containing the main radiation source, in spite of signs prohibiting entrance without clearance. In some large plant areas I have seen other workers relaxing during noontime on the roof or against the wall of a powerful radiation source, while all the rest of the available space was unoccupied. If management suddenly improves or rectifies the situation with warning signs and barricades, there is a tendency for some employees to try to place undue emphasis on symptoms usually unrelated to the situation.

Summary

The expanding recognition of radiation in our environment and the chances of long-range genetic damage effects are leading to legislation and codes which are well intended but which may become too restrictive. The medical profession must counteract this activity by emphasizing (1) the precautions it is taking in using radiation, (2) the great contributions radiation offers in the prevention, control and management of illness, and (3) the experience the profession can contribute to committees forming control policies.

Law suits have already been filed in which genetic damage is claimed. The outcome of these suits will set precedents, and, regardless of the decisions made, we can all expect some changes in liability insurance.

Industrial situations present some physicians with special responsibilities in evaluating safe working conditions, selecting appropriate workers for the area, and in orienting union stewards in the degrees of risk and the extent to which special job classifications should be restricted.

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Radiology FOR PRACTICING PHYSICIANS

Fibrosarcoma, Osteosarcoma and Chondrosarcoma

PAUL C. HODGES*

As I pointed out recently in a discussion of nonossifying fibroma, the patient suspected of having a malignant bone neoplasm needs the care of a team of specially qualified radiologists, pathologists and orthopedic surgeons; biopsy, while of the utmost importance, should be deferred until the patient is in the hands of such a team. The peculiar and extremely important contribution of the physician who first sees the patient is to suspect malignancy on the basis of clinical and radiographic findings and, having suspected it, to refer the patient promptly.

There are, of course, many types of metastatic and primary skeletal neoplasms as well as numerous benign bone tumors, but I shall discuss only three types of malignant bone sarcoma, namely, fibrosarcoma, osteosarcoma and chondrosarcoma.

The nomenclature of bone tumors is not well standardized, and some currently used classifications are based on the assumption that it is possible to determine the tissue from which a particular neoplasm has sprung. For example, the neoplasm which we call osteosarcoma frequently is called an osteogenic sarcoma on the assumption that it springs from bone tissue. At the University of Chicago, following the teaching of the late Dallas B. Phemister, his students in surgery, bone pathology and radiology consider it more logical and more practical to classify bone tumors on the basis of the predominant type of tumor tissue that they contain, thus avoiding speculation as to the tissue from which they may have sprung. Even for the pathologist, however, this may not be as easy as it sounds, because all three of the tumors under consideration contain all three types of tissue, namely, tumor fibrous, tumor bony and tumor cartilaginous, and he who would classify them must determine which is the preponderant type of tissue.

*Emeritus Professor and Chairman, Department of Radiology, University of Chicago, Chicago, Illinois.

Tumor Bone Versus Reactive Bone

In a typical fibrosarcoma, the amount of tumor bone is so small that it cannot be seen by x-ray, but sometimes these tumors and almost regularly osteosarcomas and chondrosar-

FIGURE 1. Fibrosarcoma of shaft of left humerus in a 40 year old woman. At autopsy the tumor itself (invisible by x-ray) was found to be a large soft tissue mass surrounding the middle third of the shaft of the humerus and invading it from the outside. This is the type of fibrosarcoma which by x-ray alone cannot be distinguished from early stage acute pyogenic osteomyelitis. Seldom are the two conditions confused, however, if physical examination and history are taken into account. One sees here neither tumor bone nor reactive bone, but simply myriads of tiny punctate areas of destruction scattered throughout the middle third of the shaft with minimal erosion of the outer layer of cortex.

FIGURE 2. Same case as figure 1, one month later. Destruction of outer layer of cortex is a little more complete, and a very small amount of reactive bone has developed in the region of the deltoid tubercle.

comas cause the periosteum of the involved portion of the skeleton to lay down so-called reactive bone much as it produces involucrum in osteomyelitis. The microscopist himself cannot always be certain of his ability to distinguish between tumor bone and reactive bone, and for the radiologist the job is much more difficult. He must make the effort, however,

FIGURE 3. Fibrosarcoma of lower end of shaft of femur in a 49 year old man, arising within the medullary canal and producing reactive bone. The intramedullary portion of the tumor is dramatically demonstrated by the destruction it has accomplished in the spongiosa and cortex; but, as in the previous case, the extramedullary portion at the lateral side of the shaft gave little x-ray evidence of its presence.

FIGURE 4. Frontal view, same case as figure 3. There has been sequestration of a portion of the lateral cortical shell, caused here by hemorrhage in the tumor rather than by infection, as in the case of osteomyelitis.

FIGURE 5. Osteosarcoma of medial condyle of tibia in a 24 year old woman. In this particular osteosarcoma, dense tumor bone has been laid down in the spongiosa and cortex and there is almost no extramedullary extension. Meningiomas, Paget's disease and some infections sometimes produce dense reactive sclerosis in portions of the spongiosa and cortex, but when such sclerosis is seen in primary bone sarcomas it usually means tumor bone rather than reactive bone and, therefore, rules out fibrosarcoma.

FIGURE 6. Lateral view, same case as figure 5.

FIGURE 7. Osteosarcoma of shaft of humerus in a 20 year old man, showing tumor bone and reactive bone in soft tissue about the shaft, tumor bone within the shaft, and partial destruction of the shaft. Amputation was done a few days later.

FIGURE 8. Osteosarcoma. Radiograph of longitudinal slice of tissue from amputation specimen of case shown in figure 7. There is a mass in the soft tissue about the proximal third of the shaft, together with tumor in the medullary canal and spongiosa. The sclerosis within the shaft is tumor bone. The radiating bone spicules in the soft tissue arranged at right angles to the shaft represent reactive bone along Sharpey's fibers that have been stretched by elevated periosteum. They have been likened to the rays of the setting sun and formerly were considered highly characteristic of neoplasm.

FIGURE 9. Typical osteosarcoma present for five months, with history of rapid growth. Family declined biopsy or surgery, but we are confident of the diagnosis. The principal tumor mass lies at the medial side of the distal third of the shaft of the femur. At the upper limit of the film the wedge-shaped shadow represents bone laid down beneath elevated periosteum, the so-called Codman triangle. Dense sclerosis within the shaft undoubtedly is tumor bone. Part of the new bone in the soft tissue mass presumably is reactive bone, and part is tumor bone. Note that for the time being the epiphysial plate has provided a barrier against the distal spread of the tumor.

FIGURE 10. Lateral view, same case as figure 9.

and presently I shall describe the criteria that he employs.

Bone Destruction

In a few cases of osteosarcoma the laying down of new tumor bone is so active that it masks destruction of the old bone, but usually in all three types of sarcomas destruction is a prominent feature, and frequently it is so severe as to lead eventually to pathologic fracture. These two phenomena, bone production and bone destruction, plus age incidence, anatomic location and clinical course are about all we have as a basis for radiologic detection of a skeletal lesion, its identification as a malignant primary sarcoma, and its classification as a fibrosarcoma, an osteosarcoma or a chondrosarcoma. As a matter of fact, these same criteria are the only ones we have to identify skeletal lesions of all sorts, and it is not surprising that our diagnoses sometimes are wrong; the remarkable thing is that so frequently they are correct.

Fibrosarcoma

Fibrosarcoma is a destroyer rather than a producer of bone, and the new bone that occasionally is seen is of the reactive type. When these tumors arise within the medullary canal, they may destroy spongiosa extensively, expand the cortex, elevate the periosteum, and stimulate it to produce reactive bone. Sclerosis of existing spongiosa and cortex by the laying down of tumor bone within them does not take place.

When fibrosarcomas are extramedullary, they usually fail to produce reactive bone and their extension into the shaft produces patchy destruction somewhat resembling that seen in the early stages of pyogenic osteomyelitis. The victims usually but not invariably are young adults. A common site is the femur at the knee. Origin is more commonly central than peripheral, and unfavorable progress usually is somewhat less rapid than in the case of osteosarcomas.

FIGURE 11. Huge neglected chondrosarcoma of right femur in a 26 year old man. This chondrosarcoma had been present for at least a year. At the time this film was made there was a small solitary metastasis in the left lung, and two months later the patient died. The enormous tumor involved the head, neck, and proximal third of the shaft of the femur and extended out into surrounding soft tissue. This sort of coarse, irregular, splotchy pattern in the soft tissue has been shown by Dr. Phemister to be tumor cartilage.

Osteosarcoma

Osteosarcoma tends to occur in children, is most common in the femur and the tibia at the knee, and is characterized by the production of tumor bone within the shaft in the external masses and frequently in metastases. On the other hand, reactive bone may be present as

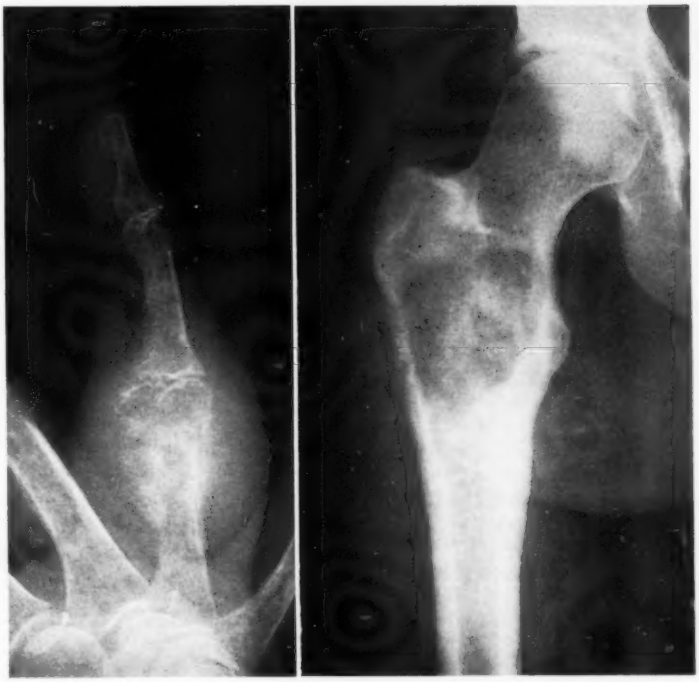

FIGURE 12. Chondrosarcoma of proximal phalanx of fourth digit of right hand in an 84 year old woman. There had been painful swelling of the digit for three years following an injury. It seems probable that this chondrosarcoma developed in an old, formerly benign enchondroma.

FIGURE 13. Chondrosarcoma of proximal end of shaft of femur in a 39 year old woman. Unlike the case shown in figure 11, this chondrosarcoma is of the central type and has not extended into the soft tissue outside the shaft. It looks like a huge bone cyst, but lesions as large as this one, particularly in adults, usually are chondrosarcomas rather than bone cysts. There has been sufficient thinning of the cortex to produce an incomplete pathologic fracture and, in the region of the lesser trochanter, tumor bone has formed at the medullary side of the cortex.

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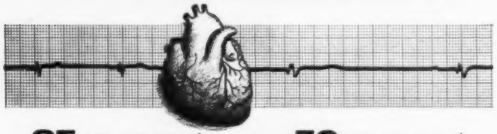

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well in large amounts and in the past many workers have mistaken it for tumor bone. Unfavorable progress usually is rapid, but occasionally wide resection of an early, sharply localized lesion leads to clinical cure, and sometimes solitary metastases respond favorably to irradiation.

Chondrosarcoma

In almost all respects chondrosarcomas are more variable than the other two types. They do not spare the younger age groups but, unlike fibrosarcoma and osteosarcoma, sometimes they make their appearance only very late in life. Any part of the skeleton may be involved, but the most common locations are the pelvis and the upper ends of the femurs and humeri.

The degree of malignancy is extremely variable. Some chondrosarcomas respond nicely to irradiation and metastasize either very late or not at all. On the other hand, there is more than a little reason to believe that benign chondroblastoma and benign enchondroma may be converted to malignant chondrosarcoma by ill-advised irradiation.

Benign chondromas, particularly of the ribs and the costal cartilages, and even some osteocartilaginous exostoses undergo malignant degeneration and become chondrosarcomas; this possibility should always be kept in mind when one of these normally benign lesions which has remained stationary in size for a long period begins to grow.

In general, the joints are strikingly immune to neoplasm of any sort, but chondrosarcoma of the sacro-iliac joint is an important exception to this rule. When it does occur it may be largely destructive with little or none of the characteristic tumor cartilage, and thus may be misinterpreted as a tuberculous or other infection of the sacro-iliac joint.

Chondrosarcomas are easy to diagnose when they contain tumor cartilage of the sort shown so dramatically in figure 11 or when they obviously have developed in an enchondroma, as in figure 12. Diagnosis is much less easy when they are central in origin and contain little or no radiologically demonstrable calcified tumor cartilage, as in figure 13.

Comments by investigators on

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– the remarkably efficient skeletal muscle relaxant, unique in chemical formulation, and outstanding for sustained action and relative freedom from adverse side effects.

PUBLISHED REFERENCES: 1. Carpenter, E. B.: Southern Medical Journal 51:627, 1958. 2. Forsyth, H. F.: J.A.M.A. 167:163, 1958. 3. Little, J. M., and Truitt, E. B., Jr.: J. Pharm. & Exper. Therap. 119:161, 1957. 4. Morgan, A. M., Truitt, E. B., Jr., and Little, J. M.: J. Am. Pharm. Assn., Sci. Ed. 46:374, 1957. 5. O'Doherty, D. S., and Shields, C. D.: J.A.M.A. 167:160, 1958. 6. Park, H. W.: J.A.M.A. 167:168, 1958. 7. Truitt, E. B., Jr., and Patterson, R. B., Proc. Soc. Exper. Bio. & Med. 95:422, 1957. 8. Truitt, E. B., Jr., Patterson, R. B., Morgan, A. M., and Little, J. M.: J. Pharm. & Exper. Therap. 119:180, 1957.

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CONDITION	NO. PATIENTS	RESPONSE			
		"marked"	moderate	slight	none
STUDY 1[1]					
Skeletal muscle spasm secondary to acute trauma	33	26	6	1	—
STUDY 2[2]		"pronounced"			
Herniated disc	39	25	13	—	1
Ligamentous strains	8	4	4	—	—
Torticollis	3	3	—	—	—
Whiplash injury	3	2	1	—	—
Contusions, fractures, and muscle soreness due to accidents	5	3	2	—	—
STUDY 3[5]		"excellent"			
Herniated disc	8	6	2	—	—
Acute fibromyositis	8	8	—	—	—
Torticollis	1	—	—	1	—
STUDY 4[6]		"significant"			
Pyramidal tract and acute myalgic disorders	30	27	—	2	1
TOTALS	138	104 (75.3%)	28 (20.3%)	4	2

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"In the author's clinical experience, methocarbamol has afforded greater relief of muscle spasm and pain for a longer period of time without undesirable side effects or toxic reactions than any other commonly used relaxants . . ."[2]

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"An excellent result, following methocarbamol administration, was obtained in all patients with acute skeletal muscle spasm."[5]

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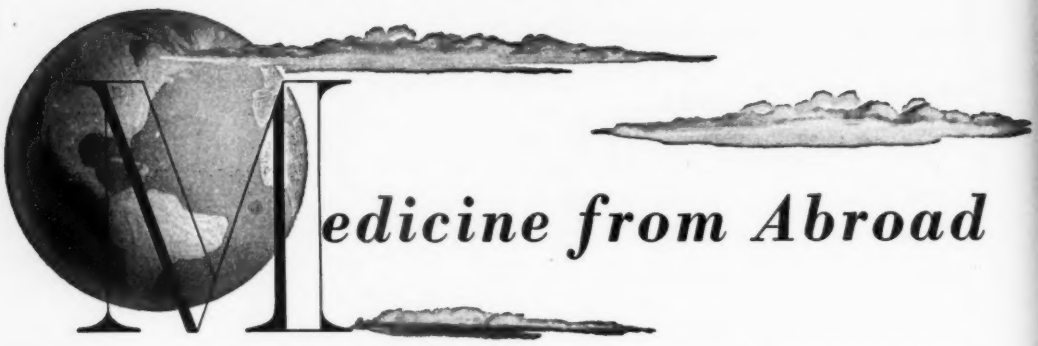
"In no instance was there any significant reduction in voluntary strength or intensity of simple reflexes."[6]

Southern Medical Journal

"This study has demonstrated that methocarbamol (Robaxin) is a superior skeletal muscle relaxant in acute orthopedic conditions."[1]



Medicine from Abroad

FROM POSTGRADUATE MEDICINE'S CORRESPONDENTS

ARGENTINA

Serum glutamic oxaloacetic transaminase in cerebrovascular accidents—At a meeting of the Argentine Heart Society, Berconsky, Lippenholtz, Litvak and Nijensohn presented the results of serial glutamic oxaloacetic transaminase (SGO-T) determinations (using the colorimetric method) in 20 cases of cerebrovascular accident caused by thrombosis (17 cases), hemorrhage, embolism and carotid thrombosis. In 7 of the 20 patients (35 per cent), there was an increase of SGO-T with maximum values between 38 and 69 units during the first week following the cerebrovascular accident; in the remaining patients SGO-T values were within normal limits. In one case, a few hours after sudden aphasia and hemiplegia occurred, the patient went into coma. The rise in SGO-T values began three days later and coincided with electrocardiographic findings of acute myocardial infarction. The patient died the following day.

A simultaneous study of GOT in the spinal fluid was made in five patients, and the values obtained were between 12 and 20 units. Only one of the five patients also had an elevation of SGO-T; he died the following day.

Contrary to the results obtained by many researchers concerning the reliability of the SGO-T curve in diagnosing acute myocardial infarction, these investigators believe that serum and spinal fluid GOT determinations are of no practical value in the diagnosis of acute cerebrovascular accidents.

Hypotensive action of chlorothiazide—Battle, Grinberg and Pronzatti reported that the administration of chlorothiazide to 60 hypertensive patients being treated with different antihypertensive drugs (hydralazine, *Veratrum*, reserpine and ganglionic-blocking agents), with and without salt restriction, resulted in a further decrease in average blood pressure in all groups studied. In their opinion, chlorothiazide has some hypotensive action per se in addition to its ability to increase excretion of water, sodium and chloride.

Vedoya, Mendelzon, Villa and Clavijo confirmed these results. They found a further decrease in blood pressure occurred when they added to the previous regimen a daily dosage of 2 mg. chlorothiazide for three days and gave a subcutaneous test dose of 6 mg. hexamethonium. There was a similar, though a less pronounced effect, when they used mercurial diuretics in the same way.

Iproniazid in angina pectoris—In a recent issue of *La prensa médica argentina*, Dr. P. Cossio reported he had administered iproniazid phosphate (MARSILID® phosphate) in doses of 25 to 50 mg. every eight hours to 36 patients who had various degrees of angina pectoris and had not responded to the usual treatment. The drug was given either continuously or for periods of three to six weeks. The determining causes and the frequency and intensity of attacks, as well as the patient's daily consumption of nitroglycerin, were checked during the two weeks prior to treatment.

In 40 per cent of the patients, the use of

(Continued on page A-74)

Now–the most widely prescribed tranquilizer[1] in sustained release capsules

Meprospan*

meprobamate (Miltown®) capsules

q. 12 h.

Two capsules on arising **last all day**

Two capsules at bedtime **last all night**

relieve nervous tension on a *sustained* basis, without between-dose interruption

"The administration of meprobamate in sustained action form [Meprospan] produced a more uniform and sustained action... these capsules offer effectiveness at reduced dosage."[2]

Dosage: 2 Meprospan capsules q. 12 h.

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1. Meprobamate is more widely prescribed than any other tranquilizer. Source: Independent research organization; name on request.

2. Baird, H. W., III: A comparison of Meprospan (sustained action meprobamate capsule) with other tranquilizing and relaxing agents in children. Submitted for publication, 1958.

Literature and samples on request

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iproniazid phosphate led to complete or almost complete disappearance of anginal pain; in 30 per cent, the frequency of the attacks was reduced to less than half and their intensity was diminished (with consequent decrease in the nitroglycerin requirement); and in the remaining 30 per cent there was no change. A significant fall in blood pressure occurred in 40 per cent of the patients. However, there were no changes in the electrocardiograms, and the results of the effort test continued to be positive, although the test sometimes could be performed without pain.

These results are explained by a selective action of the drug on muscular pain of ischemic origin rather than by coronary vasodilatation. The side effects, which were never serious but only troublesome, were controlled by stopping administration of the drug for a time, then resuming treatment using smaller doses.

Three patients with intermittent claudication and one with acute popliteal occlusion were also given iproniazid phosphate in the afore-mentioned doses. It was doubtful whether the drug relieved pain in the first condition, but the results were very promising in the second.

At a meeting of the Heart Society, Drs. Lozada, Vicario, Tempone and Muniagurra described their experience with iproniazid phosphate in 20 patients with angina pectoris, with or without myocardial infarction, and in 12 patients with peripheral arteriosclerosis and intermittent claudication of the lower part of the legs. Of the patients with angina pectoris, good results were obtained in 35 per cent, doubtful results in 15 per cent, and no results in 50 per cent. In patients with intermittent claudication, the results were unsatisfactory; there were many signs of intolerance and sometimes administration of the drug had to be diminished or stopped. No changes were found in electrocardiograms taken at rest or after effort.

AUSTRIA

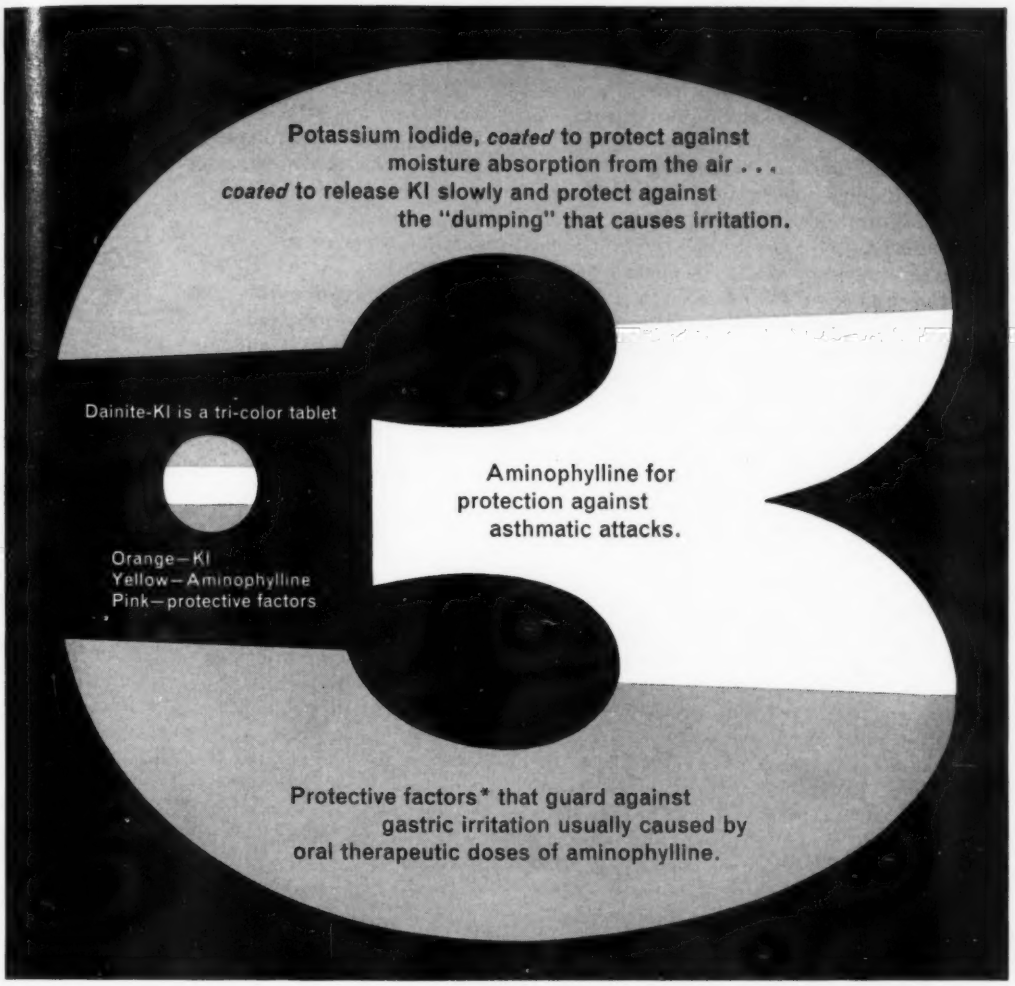
Sliding hiatal hernia in the newborn—At a recent scientific session of the Society of Physicians in Vienna, Dr. G. Felsenreich described an infant admitted to the Pediatric Clinic of the University of Vienna because of bloody vomiting and blood-tinged meconium. Roentgenographic examination revealed the typical image of a sliding hiatal hernia with ulceration at the lower segment of the esophagus. Keeping the infant in an erect position stopped the vomiting at once; he thereafter showed good progress and steadily gained weight. Eight weeks later, an x-ray examination showed an unmistakable improvement; no part of the stomach was out of place and the cardia was able to close well. Felsenreich then enumerated the hypothetical causes of sliding hiatal hernia, discussed the differentiation between a sliding hiatal hernia and the paraesophageal form of hernia, and pointed out the value of direct roentgenographic examination of infants who habitually vomit. In his opinion, the condition is relatively rare since no cases have been previously reported in Austrian pediatric literature.

During the discussion, Dr. W. Denk pointed out that while a short esophagus is seen infrequently in Europe, the paraesophageal diaphragmatic hernia is fairly common in adults. The infant described might have had a paraesophageal hernia since the esophagus seemed to be tortuous; however, this form of hernia is very seldom seen in young children, while true diaphragmatic hernias are more common, even in infants.

Dr. V. Grunberger, who delivered the infant, reported that, despite good contractions in the primiparous mother, the fetal head, which was resting on the pelvic floor, did not advance to delivery. Presentation was fronto-anterior. Since heart sounds became worse, an obstetric forceps was used and the child was easily delivered. He began to cry after a few minutes, though not very loudly. Immediately after delivery, he vomited large amounts of a slightly brownish liquid which at first was thought to be swallowed amniotic fluid. Since slight cranial injury could not be ruled out, preventive treatment with vitamin K was started at once. The vomiting did not abate, and the vomitus became increasingly sanguinolent. The infant was therefore moved to the Pediatric Clinic where the doctors first considered the possibility of a brain injury, but, as was mentioned previously, later discovered the presence of a sliding hiatal hernia. From an obstetric point of view, therefore, it is important that when a newborn child continues to vomit after birth, the possibility of a hiatal hernia as well as a head injury should be considered.

Dr. H. G. Wolf suggested that the frequency of hiatal hernia might vary according to different geographical regions, as has also been pointed out by Caffey of New York. In the case discussed, the tortuous course and the normal length of the

(Continued on page A-76)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Aminophylline for protection against asthmatic attacks.
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esophagus ruled out the congenital etiology of a short esophagus and suggested, rather, a condition secondary to shrinkage resulting from peptic ulcerations.

Functional cerebral angiography—By connecting a Phillips image-reinforcing tube with a motion picture camera, Drs. K. Gloning and E. M. Klausberger were able to film cerebral angiographs at a frequency of 25 to 60 pictures per second. The effect of various drugs on the successive passage of a radiopaque substance through individual vascular segments also could be observed. The functionally important terminal vessels, such as the arterioles, capillaries, anastomoses and venules, cannot be demonstrated angiographically, but their function may be ascertained by the length of time the contrast substance remains in the small arteries that are demonstrable (called by Lindner the "length of stay in the terminal vessels"). A prolonged stay in the terminal vessels indicates an increase in circulatory resistance, while a shorter stay suggests a reduction in the obstacles. Repetition of angiography after one to three minutes will cause no significant change in the passage of the contrast substance or in its length of stay in the terminal vessels. A dose of 40 mg. papaverine hydrochloride given intravenously produces an indefinite effect after two minutes. But, in the majority of the investigated cases, 10 mg. Duvadilan significantly shortened the length of stay of the contrast substance in the terminal vessels, sometimes by as much as 24 per cent. According to these investigations, Duvadilan also will cause a definite widening of the peripheral vessels, and will perceptibly reduce the circulatory obstacle in the cerebral terminal vessels.

Mercurial poisoning and syphilis—Madame E. Lesky reported that one hundred years ago in Vienna the question of whether mercurial poisoning was the cause of secondary and tertiary syphilis created a good deal of controversy. In 1855, Josef Hermann, then chief physician of the Wiedener Hospital, reported his theory regarding the identity of constitutional syphilis and mercurial poisoning. The subsequent debates in which Johann von Waller, Rudolf Virchow, Richard Overbeck and others participated produced the first basic data on the absorption, action and excretion of mercury in the human body. The controversy did not end until 1861 when Adolf Kussmaul published his monograph "Investigations on constitutional mercurial poisoning and its relation to constitutional syphilis," in which chronic mercurial poisoning, a "chronic poisoning with a metal," was distinguished once and for all from syphilis, " a virulent epidemic." The complete report will be published in *Deutsche medizinische Wochenschrift.*

ENGLAND

Costen's syndrome—In a series of papers published between 1934 and 1956, Dr. J. B. Costen of St. Louis ascribed the following syndrome of symptoms to temporomandibular joint dysfunction: (1) neuralgia of the second or third division of the fifth nerve; (2) pain in and around the ears; (3) a stuffy sensation in the ears; (4) pain up the back of the head and down the side of the neck; (5) headaches, chiefly of the vertex; (6) pain in the sinuses; (7) impaired hearing; (8) tinnitus; and (9) altered sensations of the tongue and throat, including changes in taste. Although Costen has modified considerably his original views, he rendered a great service in pointing out the relationship between malocclusion, temporomandibular joint dysfunction and facial pain.

At a recent meeting of the Royal Society of Medicine, Dr. George T. Hankey, president of the section of odontology, reviewed 100 of the more than 500 cases of Costen's syndrome he has treated during the last 10 years. Eighty-two of the patients had local symptoms which they could relate to joint or mandibular function. These symptoms included clicking with or without pain and occasional locking which at first was reducible but often eventually became irreducible and led to restricted opening. In the early stages, this was accompanied by pain and muscle spasm, but later it became painless after fibrous contractions or adhesions had developed. Other patients complained of recurrent subluxation, either primary or in the joint opposite the restricted one. The type of pain was either spasmodic, short and sharp or a dull continuous ache. In 18 of the 100 cases, distressing facial, head and neck neuralgias, without joint symptoms but due to mandibular displacement or muscular tension, were present. In Dr. Hankey's experience, the ear symptoms described by Costen were al-

(Continued on page A-78)

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In a sense, when you prescribe "Premarin" for a wife and mother who is suffering in the menopause, chances are you're treating the whole family. Junior, Sis, and Dad, just like Mom, can tell the difference right off.

Mother isn't just more tranquil on "Premarin" therapy. Hundreds of published reports tell us she takes a positive outlook on life. She feels *good*. And we all know that's the single most important factor for a happy home.

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most nonexistent, but the neuralgias were very real. X-ray examination revealed that 34 per cent of the temporomandibular joints were normal, 58 per cent had abnormal condylar movement, and 8 per cent showed pathologic change. Ninety-seven per cent of the patients had some form of malocclusion; 3 per cent were definitely psychoneurotic, and another 9 per cent were in a state of mild anxiety.

With regard to treatment, almost 80 per cent of the patients required prosthetic appliances. A removable plastic overlaid appliance is easily and cheaply made with a minimum of inconvenience to the patient and supplies an immediate remedy for the pain. Later, when the spasm and pain have been relieved, it sometimes can be worn less and less frequently, perhaps only at night, or discarded altogether. Some of these patients were rehabilitated by means of fixed inlays and bridges, but this type of work is time-consuming and expensive. Among the 21 patients not treated with prosthetic appliances, were those with only minor degrees of malocclusion which could be cured by selective grinding, muscle exercises and self-control. Many patients required several types of treatment. Injections of hydrocortisone into the periarticular tissues and joint cavities proved of great benefit in patients whose pain was not relieved by bite rehabilitation alone or in whom there was an established mild degree of osteoarthritis. Unilateral miniscectomy was performed on five patients, but they were treated prior to 1953.

Bradycardia—This term is applied to heart rates of less than 60 beats per minute, but care must be taken to distinguish between the true heart rate and the rate judged by feeling the radial pulse. According to the rate and underlying mechanism, the condition may be very serious or, as is usual, of no importance. In a recent number of the *Practitioner*, Dr. Harold Cookson, the cardiologist, writes that for sinus bradycardia (the commonest form, caused by a slow rate of discharge from the sino-atrial node) of moderate degree no treatment is necessary. In the exceptional case of extreme sinus slowing, a sympathetic stimulator such as ephedrine, ½ gr. (30 mg.) given orally, or methamphetamine, 10 mg. given intramuscularly, can be used, but should be employed cautiously if cardiac infarction is the underlying cause. When digitalis causes undue slowing in either sinus rhythm or atrial fibrillation, or seems responsible for sino-atrial block or nodal rhythm, it should be omitted for a time. This also applies when abnormal conduction due to quinidine occurs. Heart-block usually will only call for treatment in the complete form when severe bradycardia is giving rise to symptoms; in these cases, intramuscular injection of 5 to 10 minims (0.3 to 0.6 ml.) 1 to 1000 strength ADRENALIN® is the most effective treatment. For more prolonged effect, Adrenalin in oil can be used.

Clinical trials of drugs—A daylong symposium on the clinical trials of drugs, organized by the pharmaceutical firm of Pfizer Limited, was held recently at the Royal Society of Medicine. The chairman, Sir Charles Dodds, F.R.S., referred in his opening remarks to clinical testing as "the most burning question in medical therapeutics." Dr. J. G. Scadding, of Brompton Hospital, discussed the ethics of clinical trials. A presupposition, he said, was that full animal experiments and sometimes experiments on a few human volunteers had been carried out; a pilot trial might follow and then a controlled trial. During the course of the day's discussion it was evident that most of the speakers thought that this procedure was sound in general, though there was some disagreement on the nature of the pilot trial or preliminary clinical observations, for these could not give a decisive answer that was satisfactory to the more rigorous mathematicians. Dr. Scadding said that the advantages of using all the early supplies of a new drug in a clinical trial were apparent, but that physicians were reluctant to carry out a trial with a drug they had evidence for believing was more beneficial than its alternatives. Professor Crofton of Edinburgh said that in many respects the control group trial was the safest. In some situations, such as testing the treatment of a highly fatal acute disease, e.g., tubercular meningitis, no control group was required. But there was an area of doubt, and he considered it unethical *not* to have a clinical trial in such cases.

Dr. O. Savage, of Middlesex Hospital, pointed out that assessing the value of a drug was far more difficult in chronic than in acute diseases. With regard to rheumatoid arthritis, for example, no satisfactory method of assessing pain has yet been devised; they have given up tests of joint movement as being too unreliable; tenderness and grip provide the best objective tests in this disease. At least four methods, all largely subjective, are in current use for measuring disability in rheumatoid arthritis. Dr. I. Sutherland,

(Continued on page A-89)

Husbands, too, like "Premarin"®

THE physician who puts a woman on "Premarin" when she is suffering in the menopause usually makes her pleasant to live with once again. It is no easy thing for a man to take the stings and barbs of business life, then to come home to the turmoil of a woman "going through the change of life." If she is not on "Premarin," that is.

But have her begin estrogen replacement therapy with "Premarin" and it makes all the difference in the world. She experiences relief of physical distress and also that very real thing called a "sense of well-being" returns. She is a happy woman again – something for which husbands are grateful.

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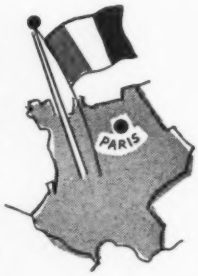
of the Medical Research Council, expressed a preference for objective measurements. The essentials of a comparative trial (he preferred this term to controlled trial) are: (1) definition of ethical aims, (2) selection of a population, (3) recruitment of enough subjects, and (4) random allocation to a series. Dr. Dudley Hart, of Westminster Hospital, observed that the results of treatment with many familiar substances, such as gold or salts, are still not precisely known. Warning about the dangers of enthusiasm in the staff concerned in a therapeutic trial, he said that a "revivalist" atmosphere could not only upset the recording of observations and the deductions to be made from them, but could lead to the production of entirely misleading data from patients whose reactions to treatment sprang from a strong expectation of cure. "Be disinterested," he said, "and consult a statistician beforehand."

FRANCE



Exposure to cold and marked drop in body temperature—In February 1956, during severe cold weather, a 49 year old man was found unconscious and nude on the floor of his room. He was admitted to the hospital in a comatose state, and examination revealed that his temperature, both rectally and on the body surface, was only 23.5° C.; he was inhaling only eight times a minute; his pulse rate was 22; his blood pressure could not be checked initially; his pupils were contracted; the tonus of his muscles was increased generally, and occasional fits of tonic spasm were seen. He was treated immediately with heating rings (infrared rays), repeated infusions of isotonic dextrose, and promethazine, pethidine and chlorpromazine; later, he was placed in 38° C. water. In two hours his reflexes returned and the tonic spasm attacks ceased; his rectal temperature rose to 25° C., but he remained in profound coma. In another four hours his temperature was 31° C. rectally, while his skin temperature remained at 27° C. At this time, he was given injections of suprarenal extract and NEO-SYNEPHRINE® and the rewarming process was continued. The patient's blood did not clot, and 12 hours after his admission he received blood transfusions. After 18 hours he began to swallow again, and after 24 hours he regained consciousness. Symptoms of pneumonia and delirium tremens were seen on the evening of the second day of observation, but both conditions disappeared in five days despite the appearance of collapse on the third day and a decubital ulcer at the sacral region. It was learned later that the patient used to drink more than 2 l. of wine a day, and that as a porter he did heavy work.

Professor Justin Besançon and his co-workers reported on this case (Semaine hôp. Paris 34:65 [January 14] 1958) and noted similarities with a few comparable cases found in the medical literature. The common features of accidental exposure to cold, resulting in lowering of the body temperature, are as follows:

Clinically, coma, muscular hypertonia and slackening of the pulse and respiration are observed. Man reacts to cold by a defense "a minima," without shivering, stepped-up oxygen consumption or shallow, quick breathing, and the peripheral parts do not freeze, but the skin and organs are cooled down simultaneously. Their rewarming is shown by a rise of the central temperature, which is a decisive factor in a favorable outcome.

Biologically, there is a noted loss of the clotting ability of the blood; a lasting drop in the prothrombin level; an initial increase in the hematocrit value which decreases the second day; an initial high level of blood sugar which falls to lower than normal during the rewarming process; little disturbance of the electrolytes; no sign of renal insufficiency, and an increase of carbon dioxide in the blood, which results in acidosis. In patients with alcoholism the liver may be changed somewhat. Marked deviations are observed electrocardiographically, such as inhibition of the centers of irritability, slowing down of the conductibility at all phases, and disturbance of ventricular repolarization.

Some reports have mentioned auricular fibrillation as a common feature of this condition, but Professor Besançon and his associates did not observe this in their patient. They investigated two principal methods of rewarming the patient exposed to cold: the gradual technic, which they employed in this case, and sudden rewarming, by means of immersion in very hot water. Both methods seem to have equally good results. They stated that the cause of death in exposure cases is an individual matter, and can be attributed to the heart, the central nervous system, or circula-

(Continued on page A-82)

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tory arrest which is caused by changes in the blood.

NETHERLANDS

Hypothermia in cardiac operations—Dr. H. W. ten Cate, Department of Surgery, University of Amsterdam, recently published the results of his experiments on the use of hypothermia in cardiac surgery (Amsterdam, Drukkerij de Hoop, 1958). Earlier experiments reported in the literature showed that young, especially newborn, animals tolerate deep body cooling better than older ones. Using animals of different species and ages, Dr. ten Cate tried to determine the degree of cooling that the animals could survive without harmful effects. The animals were first anesthetized with ether and then cooled with ice. The heart's activity was registered by an electrocardiograph, and respiration was carefully checked. When further cooling seemed unsafe, the animal was warmed with hot water and heat lamps.

When body temperature was at its lowest level, the heart always stopped and usually apnea was present. As the animal revived, the heart began to function again, usually irregularly, then resuming its normal action. The fact that the heart functioned abnormally and that cardiac arrest occurred during the cooling did not necessarily imply a poor prognosis, although the latter was influenced by the duration of the stoppage. Apnea was well tolerated if it did not last too long. After apnea had been present for some time, so-called apneic hypothermal respiration occurred in some animals. Respirations (about one or two per minute) were quite irregular; they began with a very deep inspiration with contraction of the auxiliary muscles, followed by quick and complete relaxation during expiration. Though apneic hypothermal respiration developed both in the animals who did and in those who did not survive the experiment, it seemed to influence favorably the resumption of heart action. An effort was made to keep all the animals alive, but 48 of the 130 used in the experiments died. It is not known which symptoms suggested a poor prognosis.

The experiments confirmed that the younger and smaller animals can stand lower temperatures than can be tolerated by older or heavier animals. With the larger animals, the effect of after-cooling must be considered. Cold blood stored in the skin by vasoconstriction is liberated into the blood stream when the warming-up process is started and continues to lower the body temperature for as long as 15 minutes. This can be dangerous when an increase in body temperature is urgently indicated.

Dr. ten Cate also studied the results of circulatory occlusion in 15 dogs, aged five to eight weeks, whose body temperatures were lowered to 73° F. Circulation was stopped by ligating the superior and inferior venae cavae, aorta and pulmonary artery. As soon as the heart action became impaired, the ligatures were removed, and the heart was massaged. This experiment was performed to discover whether the circulation could be stopped long enough to permit intracardiac operation. The results were disappointing. The circulation could be stopped without serious risk for three to eight minutes in an anesthetized dog with a normal body temperature, but could be stopped for only nine minutes in a dog with a body temperature of 73° F. The time gain was very small and hypothermia increased the operative risk. The author concluded that extreme body cooling, even in very young animals (and probably in very young children), offers too small a time advantage to make it the procedure of choice for intracardiac operations.

Basic science training—While studying in Salt Lake City, Dr. E. L. Noach expressed concern in a letter to *Nederlandsch tijdschrift voor geneeskunde* about the type of training in the basic medical sciences available in the Netherlands. There is opportunity for the clinician to obtain sufficient knowledge of the basic sciences, but more extensive training in this field should be available to persons who want to become physiologists or pharmacologists. Dr. Noach believes that such training should include extensive courses in chemistry, biochemistry and physics, combined with a somewhat restricted medical education. The editors of *Nederlandsch tijdschrift voor geneeskunde* agreed with this opinion, and warned the government that active scientific work in the basic medical sciences is absolutely necessary if a high standard of clinical research is to be maintained. Underpayment of scientists, poor laboratory facilities, and heavy teaching schedules were cited as factors contributing to the present situation.

The Part-time Industrial Physician; His Duties and Responsibilities

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A SURVEY made by the American Academy of General Practice has revealed that more than 90 per cent of all physicians in this country have some direct or indirect connection with industry. They see and treat employees of industrial organizations, and they are, in fact, part-time industrial physicians. These data, plus information supplied by the Industrial Medical Association, indicate that 5000 physicians spend part of each day in a plant dispensary, others spend a few hours a week, and the rest see industrial employees in their office or are on call for medical and surgical emergencies in industry.

WILLIAM F. ASHE

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Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

The U. S. Chamber of Commerce has pointed out frequently that the prosperity of our country is largely dependent on small industry and that most of our gainfully employed 66,000,000 people work in small, not in large, industries. Small industrial and commercial establishments which employ between 300 and 500 persons cannot afford, and by present concepts do not need, an elaborate, full-time medical service such as is maintained by large organizations like U. S. Steel, ALCOA, Standard Oil of New Jersey, Du Pont and General Motors. What small industry does need is excellent medical service from a part-time industrial physician who also is in private practice. Unfortunately, too often, the small industry does not get such service. I believe that labor and management want it in a vague sort of way, and that they turn to those of you who are general practitioners for help. You often fail them, not because you do not want the work or are lazy, but because you have not had the time to consider thoroughly the problem of providing properly for their needs. The

purpose of this brief discussion is to consider this problem with you. We shall try to answer the following questions:

1. What does small industry need from doctors?

2. How many doctors provide that need and increase rather than decrease their prestige in the community?

The function of an industrial physician is to study the employee in his occupation in order to prevent disease and injury and to promote optimal health, productivity and social adjustment. This applies to all employees from the gatekeeper to, and including, the president. The doctor is not concerned with company policy or with factional disputes between management and the labor force. He is concerned only with the health of the employees. Industry needs your help for the following purposes:

1. Preplacement physical examination.

2. First aid and preventive medical training programs.

3. Analysis of real and potential environmental hazards and recommendations for their control.

4. Periodic health appraisal of selected employees exposed to special hazards.

5. Reduction of absenteeism.

6. Emergency care of sick and injured employees.

7. On-the-job rehabilitation.

Preplacement Examination

Industry is in business to make money. It need make no apology for this fact, and our prosperity depends on it. Industry's most expensive item of cost is manpower. Industry needs the physician to help in the selection of its manpower and to preserve the effectiveness and productive efficiency of the manpower at an optimal level. We can do this very well, and can thereby help industry to save money. We also can help the employee by directing him to a job best suited to his abilities and by keeping him on the job and productive for the longest possible time.

In order to make a proper preplacement physical examination, it is necessary to know three things, two of which many part-time industrial physicians never take the trouble to learn:

1. What kind of a job is the particular man being considered for?

2. What kind of a man does the job need?

3. Is the man physically and psychologically constituted to do the particular job?

In order to make the examination properly, you will have to go into the plant with the general manager and familiarize yourself with the physical and psychologic requirements of every job in the place. You must do so periodically to keep up with changes. You must sit down with the personnel manager and work out a code which will show you that a given man is being considered for a particular type of work. Your file must contain notes about the requirements for this type of work, and you must examine the prospective employee on the basis of these requirements. If this procedure is followed, you will be able to tell the personnel manager one of the following things after you have completed the examination:

1. The prospective employee is suited for the job for which he is being considered.

2. He is unfit for that job, but could do other types of work.

3. He has an ocular, aural or dental defect which makes him unfit for the job, but he can be employed if the defect is corrected.

4. He is unfit for employment.

After one of these recommendations has been made, your responsibility in the processes of employment stop. You do not hire or discharge. This is the responsibility of the management. The plant manager occasionally may hire an employee over your protest, but at his own risk. If he does, you occasionally will have the pleasant experience of saying, "I told you so." The purpose of the preplacement examination is to find the right man for a particular job. It rarely is done to exclude a man from employment. Careful job analysis permits the hiring of many handicapped persons, who often make superior employees.

Training in First Aid

In any industry in which there is not a full-time industrial physician, it will be necessary for someone to give first aid to injured em-

ployees. You, as the company medical adviser, should train nurses, foremen and supervisors to render such aid. For example, if a man gets caustic in his eye and if first aid is rendered by a fellow worker, recovery will occur without the formation of a scar. On the other hand, if the injured employee is brought to your office without first aid, he probably will lose his eye. The "American Red Cross First Aid Textbook" may be used as a guide in training employees, but emphasis should be given to the immediate treatment of those injuries which they believe will occur most frequently.

If there is a nurse in the plant, she should know the limits of her responsibilities. You should give her a set of standing orders which cover what she should do. Never permit her to assume medical responsibilities without a signed order to do so. If you do not have a written set of such orders, Dr. Edward Holmblad, Executive Secretary of the Industrial Medical Association in Chicago, will be glad to send you a model set.

Environmental Hazards

In every plant, there are real and potential hazards to health. In a small foundry, these hazards include silica dust, heat, and burns caused by hot metals and grease. If soft metals are used, there is the possibility of poisoning by lead, zinc or cadmium. Acids are used for cleaning metals, and chlorinated hydrocarbon solvents are used to remove grease. It is your duty to catalogue these hazards and to advise the company about methods of control which will prevent injury. If you do not know how to make such a survey, you should carefully read a special article, "Survey of the occupational environment; an essential of industrial medical practice," which appeared in the *Journal of the American Medical Association*.[1] It will improve immeasurably your ability as a potential industrial physician. The Industrial Hygiene Division of your State Health Department (the Labor Department in New York and a few other states) is willing and has the tools to help you analyze these hazards and to control them within safe limits, usually at no cost to you or your employer. Both the A.M.A. Council on Industrial Health and the Industrial Medical Association are eager to help you formulate sound recommendations for management's consideration. Such standard texts as "Modern Occupational Medicine" by Fleming, D'Alonzo and Zapp[2] and "Manual of Industrial Medicine" by McGee[3] will be helpful guides.

Periodic Health Examinations

If there are special hazards, whether they be physical or chemical in the case of plant workers or emotional stress in the case of executives, it will be necessary to examine certain employees periodically. The type of the hazard determines which persons should be examined and the nature and the frequency of the examinations. The examination may consist only of a leukocyte count if the worker is exposed to benzene, or only of examination of the urine for the presence of lead if the worker is exposed to this metal. In other instances, a thorough medical examination will be necessary.

These examinations should be performed regularly, and accurate records of the results should be kept. In a nail mill, one of the chief hazards is noise, which may impair hearing. An audiogram should be made at the time of the preplacement examination, and audiograms should be made periodically thereafter in order to determine whether any permanent loss of hearing is developing. In some instances, these audiograms will have to be made only infrequently; in other instances, they will have to be made every month. Careful comparison of the audiograms made over a period of time will provide the only means of determining whether a permanent loss of hearing is occurring.

Absenteeism

In all plants, there are a few employees who are chronically absent from work. The reasons for their absence are usually emotional or socio-economic. The personnel department knows who these employees are. The industrial physician should interview these employees carefully and, if necessary, frequently. He should find out why they are chronically absent from work, and he should guide them in

the proper direction to correct their problem. The same procedure applies to the so-called accident-prone group. Accident-prone employees often are like square pegs in a round hole. An understanding of their problem often will suggest the solution and will cure the accident proneness, which is not a fixed physiologic condition.

No employee should be discharged until a termination physical examination has been performed. His unsatisfactory performance may be due to an unrecognized physical illness that can be corrected.

Treatment of Occupational Diseases and Injuries

If a worker becomes ill or is injured in the plant, his initial care and disposition should be handled by the company physician because he is the only one in the community who knows the man's job and the real nature of the hazards responsible for the illness or injury. The worker has the right to choose his own doctor for definitive care. You should permit him to do so without protest (it will not hurt your practice), and you should give the doctor any information which may help him. You should tell him what your findings are, what your suspicions are, and how to prove a definitive diagnosis. An industrial physician becomes rather provoked when an outside physician, unadvised by the industrial physician, makes a diagnosis of lead poisoning in a case in which a painter has abdominal colic, when the industrial physician knows that there is not a single milligram of lead in the paint that the man has been using.

When a sick or injured employee is ready to return to work, the plant physician should examine him in order to determine whether he is able to do his regular job. The plant physician knows best what the man does, and whether the work is light or heavy. He also knows to whom to talk in the plant in order to assure that the man may have necessary time for rehabilitation. Too often, the family physician, who knows nothing about the man's job, writes, "give him light work," without realizing that the job the man knows best may be the lightest work he can do.

Rehabilitation

Men who are injured at work (or while off duty) are rehabilitated best and most rapidly if they have something useful to do after a proper period has been allowed for healing. This is especially true in cases of fracture or sprain. It is frequently possible to get a man back on the job very soon if his work is carefully geared to his capacities and if facilities for continuing on-the-job therapy are available in the plant. Heat treatment, whirlpool baths, diathermy, etc. are all useful for this purpose in the plant. Orthopedic surgeons like to prescribe on-the-job therapy if they know that their directions will be followed. This procedure results in better and quicker rehabilitation, in less loss of earnings for the employee, and in less cost to the employer. It is good practice, whereas sending the man off on an unsupervised fishing trip to Florida may be bad medical practice and a breach of faith with industry.

Remuneration

It will be quite evident by now that much of the work that an industrial physician must do in the plant is not directly concerned with the care of patients. One cannot reasonably get paid for such service on a fee-for-individual-care basis. It is necessary to find a new formula, which may be on an hourly, weekly or monthly basis. Unfortunately, many physicians do not have a very clear idea of what they should be paid on this basis, or they have a warped idea of how much industry can afford to pay for medical service. Industry is very willing to pay for value received and it is not niggardly about doing so. It will not, however, stand for gouging.

The part-time industrial physician should be paid for the time that he spends on the job. He should spend as much time as the situation warrants. He should be paid well enough so that he will not be losing money when he is doing work at the plant which is not concerned directly with the treatment of sick or injured employees. A very simple way to determine what you should be paid is to divide your gross income from your last year of full-time private

practice by 300 (working days) and then by eight (hours). This will determine what you should be paid per hour. If you charge 50 per cent more for emergency night calls in private practice than you do for day calls, you should do likewise in industry. This is your fair fee, and industry will pay it for service rendered. This type of charge procedure makes your industrial work as important as your office or hospital work, and it will assure that each will receive an equitable share of your time.

A word of caution here may be worthwhile. The source of a doctor's income does not make him the slave of his employer. His sole concern is the health, safety and productive efficiency of everyone who works in the plant. Who pays the bill is incidental. Don't get into factional disputes or take sides with labor or management. Be a good weeping wall for both if they need it. Always try to maintain the same confidence in your industrial work as you do in your private practice. The medical records are yours. You are no more at liberty to show these records to the personnel director, general manager or union steward than you are to show your private records to them.

Conclusions

If the part-time industrial physician will pattern his practice along the lines which have been described, he will find that his industrial practice is stimulating and rewarding, he will develop a resurgence of the respect for the medical profession in his community, which has been lost in our generation, and he will take pride in his contribution to the great industrial prosperity of the nation. He no longer will feel a little bit like a parasite on its periphery. Finally, he will be contributing to free enterprise in medicine and industry. He will be stopping the leak in the medical dike which is leading toward socialism.

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HANS SELYE, M.D.

Professor of Experimental Medicine and Surgery, University of Montreal, Montreal

Special Medical Problems in the Care of the Elderly Patient

AUSTIN B. CHINN*

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AUSTIN B. CHINN

BEFORE discussing medical problems in the care of the elderly patient, it is appropriate to say something about the word geriatrics. The numerical increase in the old age population of this country, as well as that of the world, is knowledge common to all. With this increase in the number of older people, an increase in the number who become sick quite naturally follows, and there appears to be a growing belief on the part of the general public that the medical care of these oldsters should best reside in the hands of a specialist or so-called geriatrician. That this is a growing tendency is supported by the fact that at least one hospital identified with the medical management of elderly people very frequently receives requests by letter and telephone from the lay public to provide the name of a geriatrician or a specialist in old age. Some believe this to be very undesirable if not a dangerous trend, for it predisposes to the separation of medical care of the elderly patient into a separate compartment of medicine, and, in turn, specialization. I believe that of all the many aspects of health care which should be managed by the family's general physician, none is more vitally necessary than the care of the older person.

It seems to me that the medical profession should, therefore, vigorously resist this particular trend to specialization by first questioning the philosophy of geriatrics as such.

Critics of this attitude hold to the view that there is as much reason for geriatrics to be a separate discipline as, for instance, pediatrics. Issue can be taken with this, because in the case of infants and children there are many technics and a few diseases which are peculiar

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to children and which may require specialized knowledge and training. On the other hand, there are no known technics or diseases which are peculiar to old people. Vascular diseases, pulmonary insufficiency, the arthritides, various infections and new growths are not limited to old age. It is true that involutionary changes are probably more prominent in the 60s than they are in the 40s. There is, for instance, often loss of lean body mass, decalcification of bones, and atrophy of some tissues and loss of others. Changes in functions also certainly occur, particularly in various glandular systems, but these changes in structure and function almost certainly come gradually over a period of many years and are not enough to lead to another secluded compartment of medical theory and practice to be penetrated only by persons with some alleged specialized knowledge.

If the word geriatrics is necessary in our language, let us speak of geriatric medicine, but do not let us be led into the notion that study of illnesses in the elderly person should in any way be separated from the great common body of knowledge of general medicine of which it is so important a part.

To return to the discussion of medical problems in the elderly patient, let me say at the beginning that a particular attitude on the part of all health workers concerned is most necessary. It seems that persons working with these age groups must, in themselves, believe what they are doing to be of vital importance and remunerative not only to the individual patient but to his family and even to the community as a whole. A feeling prevailing among them that efforts expended for the old and sick are remunerative beyond humanitarian rewards is almost certain to promote an atmosphere of vigorous spirit and a climate of anticipation for the future. This applies not only to doctors but to the nursing profession and those other health professions of clinical psychology, medical social work, physical and occupational therapy, and so forth.

It is the common experience of all that attitudes of people working with old persons are very rapidly transferred to their patients. The extremes of purposefulness and indifference may very easily result in an easily managed situation on the one hand and chaos on the other. An objective purposefulness, garnished with patience and understanding, is completely necessary for effective care of the old sick person, and without it the most elaborate physical resources are likely to lead to nearly nothing.

As a beginning, therefore, it appears as if a very special attitude is the first requisite in the care of these patients, and it should be emphasized that this special attitude must extend among all health workers, from doctor to nurse's aide and orderly; indeed, it may be said to be as important in the orderly as in the doctor.

A second large and particularly frequent problem is that physical or mental illness or both in these patients is more often than not accompanied by social illness. Very obviously, having two major classes of sickness in the same patient at one time magnifies the problem, not arithmetically, but geometrically. It is like having two major systems very sick at the same time, which, indeed, occurs more often than not in old people.

As an illustration, we may have a patient in whom a hemiplegia from cerebral thrombosis has occurred, with immobilization. Urinary tract infection sets in, skin vitality is lost with development of decubiti, mental disorganization takes place, and, on top of it all, social sickness. Inadequate housing, nursing and money become manifest, and desperate explosive family relationships develop. This situation very obviously provides special problems of a considerable magnitude, and the doctor finds himself called on to sit on top of them all, holding the lid down as best he can. It is not so much that the nature of each problem is so large, as that there are so many of them.

In the younger person, such multiplicity is a rare and catastrophic occurrence; in the old, it is common, and is too often casually looked on until it happens to affect personally those who are indifferent. Then it becomes quite another matter. Desperate means are employed by those in positions of responsibility to resolve the many difficulties, and all too often

escape is sought by ignoring the reality of the situation. The procurement of even reasonable physical facilities to meet such problems may be a very harassing experience.

With this multiplicity of abnormalities—physical, psychiatric, social, environmental and economic—the delivery of adequate health needs to the elderly sick person calls for services from many disciplines. The position of the medical doctor in the middle of all this is obviously first to take care of the patient's physical needs. But, at the same time, he must act as coordinator for the psychiatrist, nurse, social worker, physical therapist, or whoever else may be called on to deliver service. This is both the doctor's privilege and his duty, for traditionally he is not only looked to for leadership, but he is also legally responsible. It is up to him to keep objectives of management in sharp focus and to see to it that the other professional people working with the patient are abreast of one another. This is sometimes laborious and time-consuming, but it is often rewarded by significant achievements.

Actually, this role of the doctor as overseer of all facets of health, though not described in medical textbooks or journals, is one of the very important and basic reasons why the medical profession is what it is. A fine physician, while treating a patient with congestive heart-failure, for instance, considers the heart as only part of his problem and does what is indicated for the total welfare of his patient. Elderly sick patients are the most perfect examples of individuals with multiple needs.

In the past five years, we have had the opportunity to evaluate and manage a substantial number of very old and very sick people in the Benjamin Rose Hospital, a division of the University Hospitals of Cleveland. Note may be made that the words evaluate and manage were used in place of the usual terms diagnose and treat. Without meaning to delve into semantics, it seems that the words evaluate and manage are more suitable to the old sick person, for there is a suggestion about them of less strident tempo and perhaps a greater inclusiveness.

Health contributions to the elderly patient in this hospital have fallen into three broad categories of activity, with considerable overlapping among them. Each patient very naturally has received proper physical appraisal, and treatment has been directed along the line of either chemical therapeutics or physical therapeutics, or both. Under chemical therapeutics may be classified medication regimens varying from that used, for instance, in the treatment of cardiac failure to that used for relief of discomfort in carcinomatosis. Under physical therapeutics may be included the modalities of physical medicine, which have consisted, in part, of muscular exercises, ambulation training, and teaching the patient technics in self-care. Such treatment has been applied to a wide range of persons varying from those needing mobilization following a serious medical or surgical illness to persons very disabled from such conditions as hemiplegia or arthritis.

Finally, we have a third group of patients admitted to this hospital with no specific therapeutic objective, but primarily for the evaluation of their environmental needs to provide optimal help or care. This evaluation is with respect to either home needs or institutional needs. As has been said, there is considerable overlapping among these three categories, for as often as not more than one will apply to an individual patient.

In the experience of this hospital, which has had to do largely with very old and very sick patients, emphasis on functional capacity of each patient has progressively grown into sharper and sharper focus. Into whichever of the above three categories the old patient may fit, the ultimate question that invariably has to be answered about each concerns the requirements of his proposed permanent living environment as dictated by physical or mental disability.

Certainly, patients who are able to exhibit certain levels of physical function, particularly with respect to their self-care, may be able to live in a less protected environment than those who are not so capable. It is because of this that, in the final evaluation of an old and disabled person, this side of his life is of the utmost importance. What these patients are able to do or not do more often than not de-

TABLE 1

FUNCTIONAL ACTIVITIES

1. Doing personal toilet
2. Eating
3. Bathing
4. Dressing
5. Tying shoes
6. Transferring technics
7. Walking
8. Using toilet
9. Being continent
10. Climbing stairs
11. Handling braces
12. Homemaking procedures

termines whether they may return home to live with relatives, on the one hand, or be institutionalized, on the other.

This considerable emphasis on functional activities of the elderly person has stimulated us to collect and record data relative to various physical capacities and a number of environmental factors as are manifest at intervals in the course of some long-term illnesses. We are of the opinion that the collection and analysis of such information during the course of illnesses can be a valuable tool in studying the effect of physical or mental defects on function, and may lead to important conclusions with respect to management. Equally important is the periodic collection of sociologic information with respect to living environment, economics and family stresses, which may reveal how the impact of long-term illness in the old person is most keenly felt in these areas.

To illustrate what is meant by functional activities, it might be of interest to discuss briefly some information collected about a few patients with cerebrovascular accidents who were studied in this hospital. Most of them had had cerebral thrombosis, with a scattering of cerebral hemorrhage or embolism.

Table 1 lists the 12 functional activities about which information was collected from each patient at intervals during the course of the illness. Great care was exercised in determining and recording at specified times following the onset of the sickness whether the patient under study was (1) able to perform these functions alone, or (2) was able to perform the functions with the aid of another person, or (3) was not able to perform the functions at all. Figure 1 is a follow-through chart in 49 cases in which patients were admitted to the hospital because of cerebrovascular accidents. Evaluations of the functional capacities of these patients were made at the time of their admission and at intervals thereafter. Figure 2 shows the functional status of the patients in the 29 cases in which it was possible to make an evaluation six months after the cerebrovascular accident. It is quite evident that at that time many patients were severely disabled in many functions, for it was only one (feedings) that nearly all patients could perform independently. Figure 3 shows these same 12 functions in the 10 cases in which it was possible to make evaluations at both 6 and 12 months following onset of the illness. This preliminary information indicates that there is neither serious deterioration nor significant improvement in these functional activities at 12 months.

Conclusions

It is suggested that:

1. Care of the elderly patient should con-

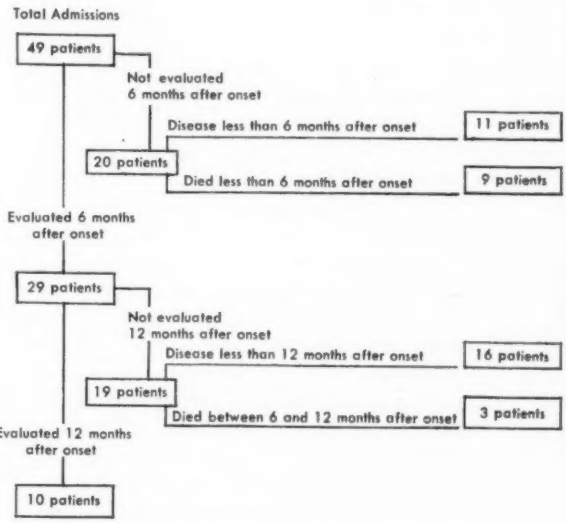

FIGURE 1. Evaluation of patients 6 and 12 months after the occurrence of a cerebrovascular accident.

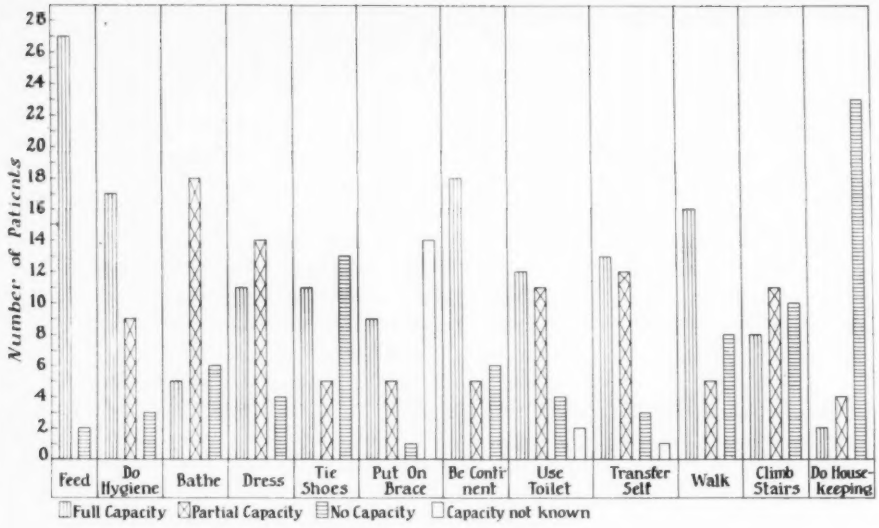

FIGURE 2. Functional status of 29 patients at end of six months.

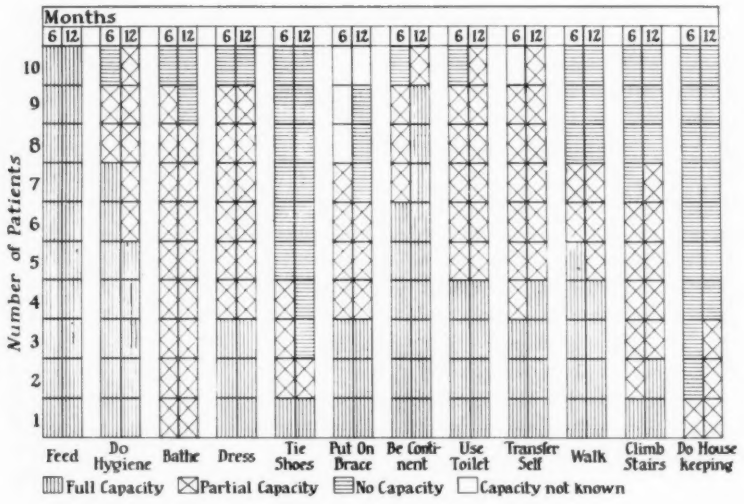

FIGURE 3. Functional status of 10 patients at end of 12 months.

tinue to reside in the hands of the general physician.

2. In order to attain the best results, an attitude of optimism and specific objectivity is quite necessary on the part of all persons working with the aged sick.

3. Because of the multiplicity of problems —physical, mental and social—so often associated with the elderly patient, services from a variety of sources have to be called on.

4. Because of the doctor's special position, it falls on him to coordinate the activities of all members of the health team.

5. The study of long-term illness may very profitably include periodic evaluation of the functional and environmental status of the patient, with the end in view of obtaining better management.

Toxicity of Local Anesthetics

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FEW potentially hazardous drugs are used as thoughtlessly, as indiscriminately and with less knowledge of their applied pharmacology as are the local anesthetics. Statistics of the number of deaths and near catastrophes from the misuse of these drugs are not available. Most difficulties arising from the use of local anesthetics may be prevented by the application of basic pharmacologic principles and by observing a number of well-defined precautions.

Untoward responses to local anesthetics are of two types, local and systemic. Transient or permanent damage to tissues results from local toxicity. The accepted drugs in current use have stood the test of time and, if used in the recommended manner, are not locally toxic. It must be remembered, in this connection, though, that local changes may also result from causes other than the drug, such as contamination, the addition of other drugs to solutions, deterioration, and so on.

The systemic type of reaction is due to the presence of an excess of the drug in the circulating blood. Irrespective of the site of injection, a local anesthetic drug is ultimately absorbed into the blood stream, after which it is detoxified and eliminated. The longer the drug remains in contact with a nerve, the longer the blockade, the slower the absorption, and the less the possibility of a reaction. Ordinarily, after induction of regional anesthesia with a given drug, the concentration of the drug in the blood is far below the toxic concentration, and no systemic effects occur. When the concentration in the circulating blood exceeds the tolerable level, symptoms of toxicity appear. These are referred to as a reaction. The more vascular an area into which the drug is injected, the more rapid the absorption. Absorption is more rapid from the scalp, which has an excellent blood supply, than from the cutaneous areas of the back

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where, for example, it is less. Reactions, thus, may be avoided by limiting the total quantity of drug used and by retarding absorption by such means as adding vasoconstrictors or using dilute solutions.

The protocols of cases in which local anesthetics have caused death suggest that reactions are most frequent after topical applications to the mucous membranes. The problem of reactions following the topical use of local anesthetics is an old one. It was of such concern that, in 1924, a commission was delegated by the American Medical Association to review the status of the then available drugs and make recommendations concerning dosage and technic of usage. Although the situation has improved considerably since submission of this commission's report, preventable deaths still occur. Seevers[1] has made the observation that more people die of local anesthetics than of any other group of drugs. Perhaps the problem does not appear to be one of great moment because deaths occur sporadically in many areas in the hands of many users of these agents.

Meager data are available on the concentration of local anesthetics in the blood after their absorption. Available data indicate that absorption occurs far more rapidly from mucous surfaces than it does from subcutaneous tissues. Woods, McMahon and Seevers[2] studied the metabolism of cocaine in dogs and rabbits. The drug was administered orally, subcutaneously and intravenously. These investigators found that little, if any, of the drug was absorbed from the stomach. They did not study the absorption of the drug from the pharynx, trachea, bronchi and other mucous surfaces, where it is used most often in clinical practice.

Steinhaus[3] reported the results of an experimental study of the comparative toxicity of local anesthetic agents. This study revealed that these agents are absorbed rapidly after their intrapulmonic instillation. In this study, Steinhaus and his associates did not determine the concentration of the anesthetics in the blood, but relied on manifestations of overdosage as an index of absorption.

In the laboratory of the Louisiana State University School of Medicine, we have studied the concentration of tetracaine, cocaine and benzocaine after they were applied topically to the pyriform fossa, trachea and bronchi, and we have compared the concentrations of the respective drugs with the concentrations observed after the drugs were administered rapidly and slowly by the intravenous route and after they were used for the infiltration of subcutaneous tissues.[4] Comparisons were made by using a fixed weight of the drugs. The concentration of the drugs in the blood increased abruptly when they were injected rapidly by the intravenous route, and the peak concentration occurred within two minutes.

When the same quantities of the respective drugs were used for infiltration of subcutaneous tissues, their presence in the blood was barely detectable at the end of 20 minutes. After the drugs were applied topically, their concentration in the blood was one-third or one-half as great as it was after they were administered rapidly by the intravenous route, and the peak concentration occurred within five minutes. Epinephrine and norepinephrine do not retard the absorption of these anesthetic agents.

When tetracaine was administered in a 4 per cent and in a 2 per cent solution, there was no difference in the concentration of the drug in the blood so long as the total number of milligrams of the drug applied to a given area was the same.

The same results were obtained when 4 per cent and 10 per cent solutions of cocaine were used. The basic form of both cocaine and tetracaine was absorbed as rapidly as the solution of their salts. When these agents were incorporated in a water-soluble cream base and applied to the mucous membrane, they were absorbed rapidly and with ease.

One often hears the statement that a 10 per cent solution of cocaine is less toxic than a more dilute solution because the more concentrated solution has a more intense vasoconstrictor effect and thus retards absorption. Our studies indicate that there is little difference in the concentration of the drug in the blood after the use of either of these solutions. When benzocaine crystals were suspended in a 4 to

10 per cent aqueous solution of cocaine and applied to the pyriform fossa, the benzocaine was absorbed just as rapidly as was an equal amount of benzocaine when used alone. If the cocaine had produced vasoconstriction, it would have retarded the absorption of the benzocaine. Studies are being made on the absorption of anesthetics from other areas of the body.

The term potency as applied to topical anesthetics is not easily defined. Tetracaine is 10 times as potent as procaine on a milligram for milligram basis. Thus, 1 mg. of tetracaine should produce the same degree of blockade as 10 mg. of procaine. On theoretical grounds, one would use one-tenth as much tetracaine. However, the duration of action of tetracaine is twice as long as that of procaine. Potency and duration of action do not parallel each other. Ordinarily, 1 gm. of procaine is the maximal quantity recommended for infiltration and perineural injection in an adult. On such a basis, it would follow that 100 mg. of tetracaine would be the maximum to use for infiltration. This, however, does not apply to topical application, because the absorption from the mucous membranes is more rapid than after subcutaneous injection. The total quantity, therefore, should be less than that recommended for infiltration or perineural injection. How much less is difficult to say, since it depends on the area and vascularity of the mucous surface. Cocaine is approximately five times as toxic as procaine. On theoretical grounds, the maximal amount of cocaine used at any one sitting should not exceed 200 mg. The dictum "use the least amount of the most dilute solution to obtain effective anesthesia" is the best one to follow.

One must remember that there is a latent or lag period from the moment a drug is applied to a nerve fiber until the effect is fully established. This is especially important when anesthetics such as cocaine and tetracaine are employed on the mucous membranes. As many as five and often as many as 10 minutes may elapse before full anesthesia is obtained. Clinicians are either unaware of this latent period, or become impatient and tend to ignore it and commence surgical manipulations before anesthesia is fully established. The anesthesia is usually inadequate, and a second application is often made before the first one has had an opportunity to exert its effect. It can be seen how such a practice readily leads to overdosage. As a rule, the longer-acting drugs manifest a longer latent period.

Overdosage affects the nervous system, or the vascular system, or both. Most physicians are generally aware of the effects of overconcentration of local anesthetics on the central nervous system. They are less familiar with the effects on the circulatory system. Usually, one system or the other is affected, but one must remember that both systems may be affected simultaneously. As a rule, the central nervous system appears to be affected more frequently than the vascular system. The majority of injectable local anesthetics, even though they differ chemically, are similar from a pharmacologic standpoint and in regard to their systemic toxic effects. As a rule, if the concentration of the anesthetic in the blood rises abruptly and exceeds the toxic concentration, it causes stimulation of the nervous system. The stimulation is usually from above downward, that is, the cortex is affected first, then the subcortical centers, then the midbrain, and finally the medulla. Medullary depression characterized by respiratory failure may, however, occur simultaneously with convulsions. Excitement, apprehension, disorientation, nausea and vomiting usually precede the convulsions.

Frequently, these prodromal symptoms are termed hysteria by physicians who are not familiar with symptoms of toxicity of local anesthetics. The severity and duration of the convulsions vary with the chemical nature, the quantity, and the rapidity of absorption of the drug, and with the susceptibility of the patient to the drug. Massive amounts infused intravenously cause fleeting convulsive manifestations which are followed by a paralytic or depressed phase. The paralytic phase is characterized by coma, complete loss of reflexes, apnea and circulatory failure.

Convulsions may be controlled by drugs which depress the central nervous system. Since the ultrashort-acting barbiturates are

potent and act rapidly, they are ideal to control convulsions. Thiopental sodium (PENTOTHAL® sodium), hexobarbital sodium (EVIPAL® sodium) and thiamylal sodium (SURITAL® sodium) are used as surgical anesthetics, and they are readily available in the operating room. Secobarbital sodium (SECONAL® sodium), pentobarbital sodium (NEMBUTAL® sodium) and amobarbital sodium (AMYTAL® sodium) are preferable for office or outpatient use. These are available in sealed ampules for immediate injection. Thiopental sodium and other ultrashort-acting barbiturates are dispensed in powdered form. In an emergency, valuable time is often consumed in preparing solutions.

A three or four minute latent period precedes the peak of action of most short-acting barbiturates. An estimated dose is administered intravenously, and then sufficient time is allowed for the drug to act before an additional quantity is injected. During this latent interval, excitement and convulsions may persist. Still, additional barbiturate must be withheld until one is certain that more is needed. Barbiturate overdosage may result if administration is continued during this latent period. Barbiturates merely antagonize stimulation of the central nervous system. They should not be used when the reaction is manifested by depression, coma, or respiratory or circulatory failure. Barbiturates do not neutralize local anesthetics, nor do they hasten their detoxication or elimination. Long-acting barbiturates, such as barbital, phenobarbital and butabarbital sodium (BUTISOL® sodium), are less effective than short-acting barbiturates and should be used only when more potent and rapid-acting compounds are not available. Other hypnotics, such as chloral, tribromoethanol, paraldehyde and the narcotics, are not clinically suitable as antagonists of the central nervous system.

Stimulation of the central nervous system may merge into a depression which often causes apnea and circulatory failure. Artificial respiration must be instituted immediately under these circumstances. A depressed state may develop without excitement or convulsions after absorption of certain drugs. Lidocaine hydrochloride (XYLOCAINE® hydrochloride), for example, causes sleepiness and drowsiness which are frequently accompanied by amnesia. After the rapid absorption of tetracaine, a comalike state accompanied by syncope frequently occurs. Depression of the central nervous system occurring without convulsions, respiratory depression and changes in the pulse or blood pressure requires no therapy except watchful waiting until the symptoms disappear.

Local anesthetics may decrease cardiac output by primarily depressing the myocardium. Besides, they cause local vasodilatation, which gives rise to varying degrees of hypotension. An extreme degree of hypotension may be due to a combination of both cardiac depression and vasodilatation. Myocardial depression without vasodilatation is usually characterized by a slow pulse, a lowered systolic blood pressure, and a reduced pulse pressure. Vasodilatation causes a decrease in systolic, diastolic and pulse pressures. The onset of a circulatory type of reaction may be abrupt. Pallor, tachycardia, syncope and complete disappearance of the pulse and blood pressure may suddenly occur. The onset of the less severe reactions is slower and the circulatory system deteriorates gradually. The patient may become drowsy and pass into a comalike state. Such reactions have been incorrectly designated as idiosyncrasy or sensitivity. They are, however, caused by overdosage as a result of failure to observe basic principles and precautions outlined for using local anesthetics.

Intravenous administration of vasopressor agents (ephedrine, desoxyephedrine, methoxamine and phenylephrine) overcomes the hypotension. When the circulation appears to have failed completely and the presence of cardiac arrest is suspected, massage simultaneously with artificial respiration is indicated without delay. Circulatory depression occurs more readily in patients who are debilitated, in those who have cardiovascular disease, or after the intravenous administration of local anesthetics for prophylaxis for cardiac arrhythmias during operation. In debilitated and acutely ill patients, the reaction is due to the combined effects of the drug on the central

nervous system and the vascular system. Circulatory failure may also occur secondary to the convulsive manifestations of a reaction probably due to the anoxia caused by an obstructed airway or laryngeal spasm, which is occasionally seen.

Not all reactions occurring during the use of local anesthetics, however, are due to overdosage. Certain patients are intolerant to drugs, including the local anesthetics. When a patient is intolerant to a drug, the average dose causes an exaggerated response. In the case of local anesthetics, a reaction of either the circulatory depressant or nervous stimulating type follows the use of less than the usual therapeutic dose of the drug. Usually, a reaction due to intolerance is characterized by circulatory depression rather than by stimulation of the central nervous system. Such reactions are erroneously ascribed to idiosyncrasy or sensitivity. The treatment is the same as that described for overdosage.

Allergic reactions follow acquired sensitization to repeated exposures to a drug. The response is that of the antigen-antibody type. The drug combines with the body proteins and becomes antigenic. Cutaneous lesions, such as eczema, urticaria, laryngeal edema, swelling of the tongue, or bronchial spasm, appear. Physicians and dentists develop allergic reactions as an occupational disease. Usually, many repeated exposures are necessary for sensitization. Patients exposed only once or twice to local anesthetic drugs seldom become sensitized.

There are, however, cases in which an anaphylactoid type of reaction develops. The patients may never have been exposed to the drug. Fortunately, such cases are extremely rare. In these cases, an infinitesimal quantity of a drug induces sudden syncope, which invariably is followed by death. Most reactions, even though they are allergic or ascribed to idiosyncrasy or anaphylaxis, are usually due to overdosage.

Stress is often placed on tests for sensitivity. The use of the intradermal wheal to prognosticate abnormal responses to local anesthetics is a traditional procedure of doubtful value. Areas of erythema are often confused with a pseudopodium formation. Thus the test is difficult to interpret when positive. Intolerance is encountered even though the test is negative, and vice versa nothing may happen if the drug is used in the face of a positive response. Patients presenting a history of syncope following injection of a local anesthetic should be studied before a local anesthetic drug is used. Patients intolerant to a drug, for example, to a drug derived from para-aminobenzoic acid, such as tetracaine, may be intolerant to other derivatives of the same acid. A patient intolerant to procaine may also be intolerant to tetracaine. Patients intolerant to drugs in one group may tolerate drugs in other groups without experiencing any untoward reactions. A patient intolerant to procaine may be tolerant to hexylcaine hydrochloride (CYCLAINE® hydrochloride), which is derived from benzoic acid.

A test which has a more logical basis than the skin test and which gives more information, particularly as to whether or not intolerance exists, is the intranasal test. A base of pulse and blood pressure values is obtained by making observations at two or three minute intervals for approximately 10 minutes with the patient in the recumbent position. One drop of the solution to be used is then instilled into either nostril or sublingually. Pulse and blood pressure readings are recorded at intervals for the next several minutes. Bradycardia, hypotension, excitement, tremors or nausea is usually indicative of intolerance. It must be borne in mind in testing a truly allergic, highly reactive patient that the test dose, be it administered intradermally or placed on the mucous membranes, and even though the quantity of drug used for testing is minute, may precipitate a severe anaphylactoid reaction which can terminate fatally. Thus, in a truly sensitive patient one may cause death by administering a quantity needed for the test.

Some reactions are in no way related to the local anesthetic drug. The side actions of epinephrine may be mistakenly ascribed to the local anesthetics. Pallor, tachycardia, or tremor and excitement caused by epinephrine may be confused with the prodromal signs of nerv-

ous system reactions. The differentiation is not difficult because epinephrine does not cause convulsions, twitchings or disorientation. The blood pressure is markedly elevated and the pulse rate is accelerated. Pulmonary emboli, fat emboli, air emboli, coronary occlusion or cerebral vascular accidents may occur coincidental to the use of a local anesthetic drug during operation. They may have been mistaken for a drug reaction by uninitiated clinicians unfamiliar with the behavior of local anesthetics. Convulsions which persist after the administration of a barbiturate or which recur at periodic intervals for several hours after the use of local anesthetic drugs are due to some other cause and not to the drug.

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INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Common Mistakes in the Management of Erythroblastosis Fetalis

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A number of independent variables in erythroblastosis fetalis make diagnosis difficult in some cases and obscure the need for treatment in others. However, early diagnosis and proper treatment are of great importance to avoid the brain damage which would otherwise complicate about 15 per cent of the cases.

The most common mistake is to assume that because the erythroblastotic baby has a high hemoglobin concentration he is in no danger. It is not uncommon for such babies to have a severe hemolytic process which is well compensated for by rapid blood production. These babies are in the greatest danger so far as brain damage is concerned.

The second most common error is to assume that because a baby is not jaundiced at birth he has little or no disease. Actually, babies never have jaundice of the skin at birth unless one counts the very minimal traces that are rarely visible in good light. Yellow vernix is not equivalent to jaundice. Thus the absence of jaundice at birth is really meaningless. Failure to look for early jaundice or to consider early or severe jaundice as a pediatric emergency results in unnecessary brain damage.

The usual price of poor management of erythroblastosis, unless one is lucky, is kernicterus, which either immediately kills the baby or leaves him a cripple. The reward for vigilance, though vigilance is sometimes laborious, is the satisfaction of having prevented cases of cerebral palsy.

Early Diagnosis of Visual Impairment in Children

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MANY causes of impaired vision and disturbances in coordination of ocular muscles during childhood originate in early infancy or sometimes before birth. These are other than congenital anomalies or arrest in development of the eye and its adnexa. In recent years, ophthalmologists have recognized these early influences on ocular disease. Two instances of previously unrecognized causes and effects may have stimulated a more careful and close look at an infant's ocular fundi.

The first of these from the standpoint of importance but not from that of time was retrolental fibroplasia or the retinopathy of prematurity. In Detroit, during 1953, this disease was four times as common a cause of blindness or severe impairment of vision as any other single ocular disease as found in the preschool group of children. It originally was described by Terry, of Boston, in 1944, who saw only the end results in the retrolental area, but it was the work of Owens, of Baltimore, about four years later, which turned attention to the retina of premature infants whose birth weight was 3.5 lb. or less. It was in these infants that the early stages of this blinding disease began to manifest itself as dilated and tortuous arteries and veins and retinal hemorrhages. Until this time, ophthalmologists had not commonly examined the ocular fundi of premature infants or made pathologic studies of these infants.

Examination showed the ocular fundus of premature infants and that of full-term infants to be different. Remnants of the tunica vasculosa lentis were found in almost every one of a group of premature infants. These appeared as black lines arranged radially near the periphery of the lens and usually disappeared when the infants attained a weight of 5.5 lb. The vitreous was hazy and did not permit a clear view of the detail of the retina. Occasionally, remnants of the embryonic hyaloid artery were noted near the optic disk or more anteriorly in the vitreous. The nerve head was pale, and the macula was not well differenti-

ated. The periphery of the retina was grayish in color, and its appearance often suggested the presence of detachment.

A study coordinated by Dr. Everett Kinsey, of the Kresge Eye Institute of Detroit, confirmed the finding that a high concentration of oxygen in the incubator or ISOLETTE® was the major cause of retrolental fibroplasia. This discovery had been made earlier by workers in Australia and England, as well as in this country. Now, the use of concentrations of oxygen no greater than 40 per cent has all but eliminated this disease. Higher concentrations should be used only when necessary to maintain life. Constant vigilance in nurseries, instruction of nurses, and careful watching of equipment, particularly in the use of the oxygen analyzer, are necessary to reverse previous practices in the free use of higher concentrations of oxygen.

The second stimulus to our thinking occurred in the early 1940s when reports from Australia linked the occurrence of cataracts in the newborn to mothers who had had German measles. It was those mothers who had the disease during the first two or three months of pregnancy who produced offspring having cataracts. When the disease was contracted after the third month, the incidence of cataract rapidly decreased.

In reviewing the development of the lens in the early months of gestation, we found that the lens fibers have begun their proliferation which continues in gradual decreasing activity throughout life and that the lens epithelium and capsule which encloses them have been developed by the end of the second month of fetal life. Maternal infections by the virus of rubella after the third month do not cause cataracts because the lens has developed to a stage where it is protected by its capsule and the early fibers of the lens have already formed. Because of these changes in the eye and other systemic malformations resulting from the placental transfer of unknown infectious elements, some physicians have recommended that women contract German measles voluntarily to produce an immunity which will protect them against the dangers to their offspring when they enter childbearing years.

Other influences of metabolism on the lens may occur before and after birth. It is known that the parathyroid glands, through their influence on calcium metabolism, may result in cataractous changes in the lens. Certain types of congenital cataracts are related to this disturbance in the mother. Rather rapidly developing lens opacities in tetany of the adult are well known. Developing cataracts in a young adult who has undergone a thyroidectomy should lead one to strongly suspect interference with parathyroid activity. The relation between diabetes and cataracts is understood. However, cataracts occur in only a very small percentage of patients who have diabetes. Generally speaking, the lens is more vulnerable in cases of diabetes in which the patients are young than it is in cases in which the disease develops in the later decades of life. There doubtless are other undiscovered disturbances of metabolism and endocrine function which influence the metabolism of the lens and thus cause cataracts. Why does a cataract suddenly develop in a five year old child who has Rothmund's syndrome?

As we know, vision differs from our other senses, being composed of three associated but separate elements: (1) the retina and optic nerve tracts, and the cortical endings; (2) the system of balance and movement or the neuromuscular system, and (3) the higher centers and multiple association pathways. Think then of vision as including the integration of all three components. A disturbance of one or part of one may impair vision.

Diseases of the retina and its posterior extensions can often be seen with the ophthalmoscope or diagnosed by studies with a perimeter or tangent screen. Those of the higher centers may or may not be as evident. The effect of emotion or mental acuity on vision is well known. The patient who has advanced cerebral arteriosclerosis may have poor perception even though retinal elements appear relatively good.

Ophthalmologists in the field of neuromuscular abnormalities have given much thought to the early influences of vision in this field. Six muscles move each eye. These must work in coordination with one another and in co-

ordination with the six muscles of the opposite eye. Any disturbance in one or more of these muscles may impair eyesight or produce disturbing and distressing side effects.

The newborn infant has vision of about 20/900, but it is the most rapidly developing sense of all, initiating other movements of the head, trunk and eye-hand associations. Until the infant is four or five months old, eye movements may be monocular. Divergent or convergent strabismus may be observed, or one eye may show nystagmoid movements. But, by the fifth or sixth month, binocular vision should be established. By the sixth month, visual acuity has improved so that objects at 10 to 20 ft. can be recognized, whereas objects can be recognized at a distance of 3 ft. when the infant is one month old. This occurs because the fovea has developed so that binocular foveal fixation is possible. A strabismus persisting after this time usually means that something has gone wrong with the neuromusculature or that the optic nerve or pathways have been impaired by disease.

Examination of these infants should be made at this time for two reasons. First, one may discover intraocular disease such as retinoblastoma. Second, in the absence of disease, the early treatment of strabismus can be much more effective at this time and becomes less and less effective as the child grows older. There is evidence to support the opinion that accommodation develops before the age of one year, possibly at six to eight months. Many types of strabismus are paralytic and due to factors operating at or before birth. These are the convergent types due to paralysis of one or both external recti. However, it is well established that some are the result of overaccommodation brought on by excessive farsightedness. I do not wait until two years of age before examining these infants. They should be examined when definite strabismus persists after the child is six months old. Children do not "outgrow" true strabismus in most cases. They do outgrow an epicanthus which many times gives one the impression of a crossed eye.

In these cases, there is a history of onset at three or four months, and examination reveals a refractive error of 4 to 6 diopters of hypermetropia. Refraction at 8 to 12 months is easier than refraction at two years so far as cooperation of the patient is concerned. Physicians are surprised to find that infants 9 to 12 months old will wear glasses without objection. They do so because objects are more clear and it is more pleasant to have eyes straight than eyes crossed.

Parents often ask if glasses change a child's vision, "weaken his eyes," or "make him more dependent on them." A lens worn in glasses bends the rays of light entering the eye to bring about a clear focus on the retina, particularly the fovea. When properly prescribed, this benefits in two ways: (1) It brings about a clear image on the retina, and (2) it relieves the ciliary muscle of abnormal effort, not normal effort. Glasses do not change the eyes. They change the direction of light rays coming into the eyes.

Excessive amounts of hypermetropia can impair vision more than can nearsightedness, the more so since both distance and near vision are reduced. These effects are in addition to the associated convergent strabismus which is produced.

In some cases, a suppression of vision in one eye develops as a result of annoying diplopia. The treatment of this condition is most effective in infancy and childhood. Chances of restoring vision by occlusion of the good eye become gradually less and less up to the age of six or seven years, when attempts at treatment produce only fair results. This is particularly true when suppression starts in infancy.

Physicians are learning more and more about the part vision plays in the developing child. It is said that 75 per cent of learning is done through vision if the child is otherwise normal. High degrees of nearsightedness and farsightedness embarrass infants and children more than they do adults. These errors in vision are sooner or later uncovered, many times not until school age, but they can be found at an early age, and the child and his parents can be saved the emotional upsets and behavior problems which arise from this source.

Some Profiles of Fever in Infancy and Childhood

PAUL V. WOOLLEY, JR.*

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FEVER has long fascinated man. Volumes have been written about it and lifetimes spent investigating it, but still it is not clearly understood. A large portion of modern diagnosis, therapy and prognosis is built around interpretation of the fever chart.

PAUL V. WOOLLEY, JR.

Body temperature obviously is the algebraic sum of the total heat produced through metabolism in muscle, brain and viscera, plus or minus the gain or loss through radiation and conduction with environment, and minus the total heat loss through evaporation. When this equation comes out with a plus number, the patient has fever. When minus, he has hypothermia. When the two balance, he has a temperature of 98.6° F.

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Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

Four general statements may be made about temperature regulation and fever:

1. So far as we know, a thermostat located somewhere in the brain governs this exquisite regulation, but no one seems to agree as to where it is. It can be stimulated from various parts of the body and, in turn, can communicate with various activators almost anyplace within the body.

2. The chief mechanism by which we increase or decrease heat loss has to be primarily by governing the amount of blood that can reach the skin, the surface, where it can be acted on by factors of radiation and of convection. Most elevations of temperature have to begin with a shutdown in loss of heat. Once that happens and the body temperature begins to rise, obviously the metabolic rate will increase, and then the metabolism itself will contribute to maintenance of the elevated temperature. Conditions such as convulsions, chills and extreme restlessness in children all go to raise the basic metabolic rate and to raise the temperature.

3. Fever, in general, is intentional. It fits in with most other useful body defenses, and

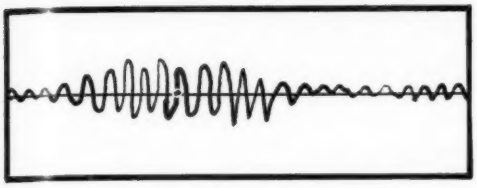

FIGURE 1. Drawing representing the fever chart of a premature infant with a gluteal abscess. Staphylococci present in blood culture.

FIGURE 2. Empyema in a newborn infant.

if we consider all its advantages and all its disadvantages we usually find fever is favorable to the patient. Currently in the era of chemotherapy we might have to modify that statement a little, but in the natural recovery from infection fever plays a tremendous role.

4. Fever is a very sensitive thing. The body guards the amount of fever as carefully as it does the normal temperature, and yet we know that theoretically and in experimental animals it is quite possible to push the temperature over 120° F.

With this background, I would like to present a few profiles of clinical problems involving fever. The illustrative material consists merely of blackboard sketches and is not exact, but it does emphasize my main points.

Fever in a Premature Infant

Figure 1 represents the most interesting of all animals, a prematurely born human being. He has little musculature, practically no insulation of any kind. One of his main problems in survival is regulation of body temperature. Therefore, it is not surprising to find that when he gets into trouble he does not respond with fever the way an older infant might do. The drawing in figure 1 shows him bouncing along, a little bit below normal, and then there is a jagged, irregular temperature; usually this is accompanied by loss of appetite and other evidence that things are not going well. One can almost get a better picture of the situation by turning the fever chart of a premature baby upside down than by looking at it right side up, because the dips go below the line about as far as the elevations go above it. This irregular temperature response in premature infants is extremely important at present, I think, with all the worry about outbreaks of infectious disease in nurseries. This is the warning that something is wrong. In the case represented by figure 1, it was merely an abscess in the buttocks from a vitamin K injection accompanied by a positive culture for staphylococci. This infection was readily controlled, and the temperature resumed the normal course in four or five days. The jagged, irregular line on the chart could have signaled the beginning of infectious diarrhea; it could have meant atelectasis, or almost anything.

Failure of Infant to React Early to Infection

We do not know what trigger mechanism starts fever on its way; foreign protein, yes, but many other factors undoubtedly are involved. Quite often a newborn infant has to learn to react with fever. Figure 2 depicts the fever chart of a full-term baby who was brought in with dyspnea. He had a perfectly flat chest, and thoracentesis yielded cloudy fluid loaded with staphylococci. Yet this baby did not know he had a disease that is fatal in 50 per cent of cases until after the show was over and he was on the way to recovery, when fever suddenly appeared. Babies can die with septicemia and never really budge their temperatures off the base line. They have to learn to run a fever just as they have to learn a lot of other things.

Overreaction to Minor Infection

The type of patient represented by figure 3 is familiar to all of you. This is the exuberant yearling. Several members of his family have runny noses and probably are a little out of

FIGURE 3. Fever chart of a one year old child with a cold.

sorts, but nothing more, and the baby's temperature rises to 103° F. Probably nothing much is done, and half an hour later the temperature is 104° and the baby has a convulsion. He is overshooting, overreacting; two years from now he will know that it would have sufficed to run a temperature of 100° F. instead of 104° F. He brings to mind the comment once made about Theodore Roosevelt: that he attacked a mosquito with the same vehemence that he did an elephant.

Usually, after some type of neighborly, grandmotherly or medical help is sought for the convulsion, the baby is bundled up and brought to the hospital. On arrival, his temperature is 107° F. A good blanket on a baby in a convulsion is a better hyperthermia setup than Mr. Kettering was ever able to invent. This is the period when we begin to worry about damage from the fever itself; this is when the baby can get what we call the "cooked brain" syndrome, which means merely a complete collapse and permanent brain damage from hyperthermia itself.

In most instances, all that is necessary is to unwrap the baby and examine him for any signs of central difficulty; if these are noted, a lumbar puncture should be done. About 50 per cent of our cases of meningitis in year-old babies are detected as a result of doing lumbar punctures in situations very much like this one. Most of the patients are found to have the common cold, and with or without treatment things settle down. This baby will learn to overcome his exuberance in a few more months, just as he learns to overcome the exuberance of feeding himself and getting into a whole variety of troubles.

Elevation of Basal Temperature

The fever chart in figure 4 represents a four year old girl who recently was sent in because of hyperthyroidism. To me, a chart of this type does not mean infection. It means that the child has transformed herself into a bird; she has a normal basal temperature of about 102° F. There are a lot of occasions when we see this picture in clinical medicine. Twice I saw it because of mistakes in preparing a baby's formula; in each instance the baby was fed a highly concentrated nitrogen mixture. Occasionally one sees it when using intravenous amino acids in an attempt to maintain alimentation. It is not unlike what one sees after hemorrhage, fracture of the kidney, rupture of the spleen, hemophilia, or bleeding into tissues. It merely means an elevation in basal temperature so that the normal temperature is no longer 98.6° F.

Overreaction to Vaccination

An interesting contrast is seen in figure 5, which depicts the temperatures of two babies of the same age who were inoculated with the same tube of smallpox vaccine. The top line represents the overreactor. By the sixth day the temperature rose to 103° F., and it remained at that plateau until about 10 days after vaccination. The bottom line is a more normal reaction.

Every few months a child is brought in because he has had this type of reaction to vaccination and someone is worried about infection or a complication. However, in reality this is simply an overreactor handling a perfectly normal vaccinia. I like to watch these children and see what they do with measles, for instance. This is the type of child who may

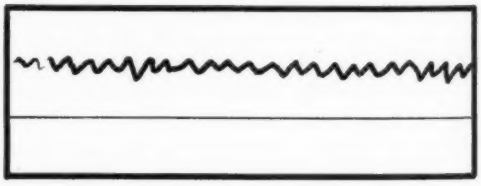

FIGURE 4. Hyperthyroidism, four year old child.

react violently to Asian influenza vaccine, and when he grows up he probably will react equally violently to his mother-in-law. This is the child for whom I like to shade the future vaccines down, divide each injection into three parts instead of giving it all at once, and watch pretty carefully to see what his pattern will be.

When we have made a diagnosis and picked out a drug which should be effective, we have by no means finished our chore. Frequent reappraisal of a patient, even when one is satisfied with the diagnosis and the basic type of treatment he is receiving, is indispensable.

Poliomyelitis

For a number of years, people talked about polioencephalitis. The chart in figure 6 would have been a good example of polioencephalitis. The trouble was that the pathologist never could find the encephalitis part of it. As these cases were analyzed, it became evident that it was not polio that was killing these children; it was the complications, especially anoxia. In figure 6 you see the usual pattern of bulbar poliomyelitis—the extreme difficulty and then a sudden drop with tracheostomy with or without a respirator, and thorough cleaning out through the tracheostomy. In other words, this is polio, but the fever is anoxia; it has nothing to do with involvement of the brain itself. This chart could be used equally as well to show the approach of addisonian crisis, in which administration of salt and water could produce a drop. It is not unlike what we see in cases of severe diarrhea and dehydration in babies, because blood volume obviously must play a large part in control of temperature if heat is lost primarily through the amount of blood that can be brought to the skin. So you can see how alert one must be.

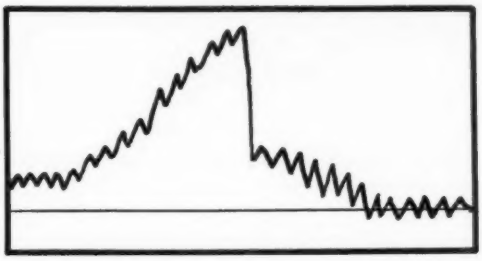

FIGURE 6. Poliomyelitis, 10 year old child.

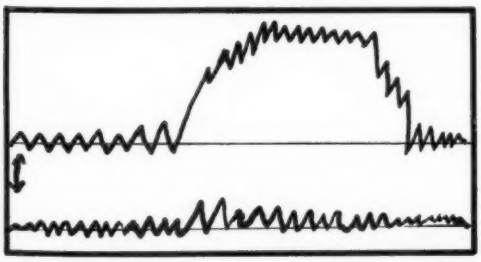

FIGURE 5. Contrasting reactions to smallpox vaccination, two infants of the same age.

Osteomyelitis

The case represented by figure 7 is much along the same lines. This is a child with acute osteomyelitis, with staphylococcic septicemia. After rapid determination of sensitivity, probably to chloramphenicol and erythromycin, therapy was begun, but there was not a dramatic change clinically. This is merely a chance to find out that all our drugs are not the entire story in treatment of a child. This patient required surgical treatment. The majority of patients with osteomyelitis still do better, in my mind, with drainage of abscess; temperature falls promptly, and the patients are comfortable, have a positive nitrogen balance, and recover uneventfully.

Meningitis

Meningitis is a constant source of confusion. A baby is brought in, and the diagnosis of meningitis is made. Almost any of the antibiotics are effective against the strain, and the infection is brought under control. Lumbar puncture is done. The fluid is clearing rapidly, the sugar is back, and there is no positive growth on cultures. To all intents and purposes the child should be well, and yet the elevation in temperature continues (figure 8). The physician begins to worry about brain abscesses, walled-off foci, endocarditis, all manner of things. In reality this is the usual path of an infant with pyogenic meningitis. It means nothing except that there still is a sterile men-

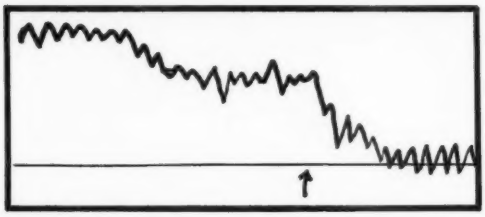

FIGURE 7. Osteomyelitis, six year old child.

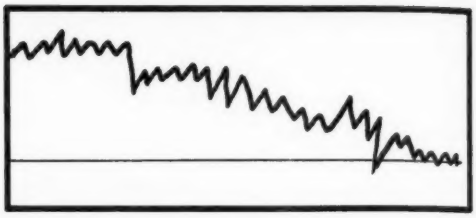

FIGURE 8. Meningitis, two year old child.

ingitis. There is no reason to give up the drugs being used or start new ones; just be calm and sit tight and let the temperature gradually return to normal. We estimate about a two week febrile period in influenza meningitis in any child under 18 months of age. Do not be discouraged; if the culture is negative and the fluid is clearing, the baby will be all right.

Fever of Undetermined Origin

When I was a resident, everyone fought over the F.U.O.s, or cases of cryptogenetic pyrexia, as I guess it was once called—in other words, fever without obvious explanation. They usually represented exotic conditions—Haverhill fever, rat-bite fever, undulant fever, all manner of obscure infections. Today the entire picture is changed. Not only is F.U.O. rarely a cause for hospitalization, but also the entire end result has changed tremendously. In the past four or five years I have seen only two children with undiagnosed fever that had anything to do with bacterial disease. One had bacilluria without white cells, and the other a carbuncle of the kidney.

Why has F.U.O. disappeared? We have better diagnostic methods. Above all, we now are able to do therapeutic tests. We can give an antibiotic to a child who has fever, and we can find out whether or not he has an infection. On top of that, our health boards have done a good job. At our institution we have not seen a case of typhoid fever for a year, and I think this is the first time in the 12 years I have been there that a year has elapsed without such a case. Five years have elapsed since we saw a case of undulant fever. A lot of these things are disappearing; the doctors are doing a much better job in trying to rule out obvious conditions, and drugs are helping tremendously.

There are just two types of consultation that I face with trepidation. One is when I receive a note that the Jones baby looks like a Mongolian idiot, and the other is a request to have a look at a six year old child who for three weeks has had fever and they do not know its cause. Usually when we see the latter child there are a few loose ends to tie together—maybe a urine culture to be obtained, maybe a blood culture, a few things that frequently are overlooked—and then we have to dig

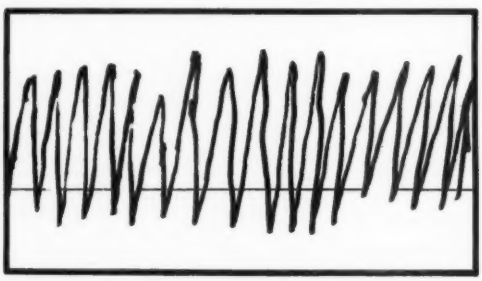

FIGURE 9. Still's disease, four year old child.

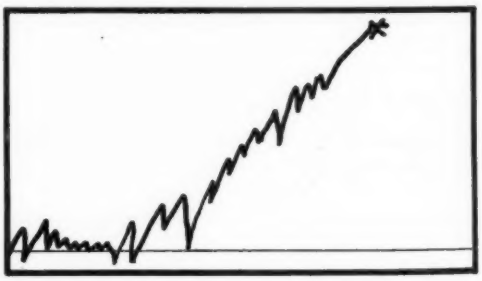

FIGURE 10. Dysautonomia, two year old child.

down and find out why the six year old, with all we have done for him, has fever. The outcome usually is not optimistic. Often these cases break down into two categories, malignant disease (neuroblastoma or leukemia) and the undifferentiated group of collagen diseases such as Still's disease (figure 9), dermatomyositis, and the childhood type of lupus.

In these conditions, bone marrow studies probably help about as much as anything. We frequently make intravenous pyelograms, because by the age of six years one of the most common malignancies is a neuroblastoma around the kidney. This usually can be seen if we have adequate visualization of the kidneys themselves. If that does not help, we probably would look for biopsy sites on the possibility of finding an arteritis that will put it in the collagen group. Another thing, of course, that can be done is empiric treatment with cortisone, which will handle either condition temporarily and give one time to find out exactly what is going on.

The spikes of temperature in these cases, often going to 104 or 105° F., are very dramatic, but they are common on pediatric services. We always hope they mean merely the onset of rheumatoid arthritis in children, but only too often they mean a malignant process.

Dysautonomia

The child whose temperature chart is depicted in figure 10 has the Riley-Day syndrome, a distressing condition known as dysautonomia. It is very probable that it will escape from all manner of temperature control, and usually terminates fatally, often with a temperature of 107 or 108° F.

I do not know how frequent central fevers are. We know practically nothing about the central type of fever, and we treat it on a purely symptomatic basis and hope for the best. When we cannot find any other reason for fever, we have come to the habit of going over on that side of the ledger. For instance, electroencephalograms often will point out a child who has epileptic seizures manifested by fever. We have not hesitated in going on to air studies in young babies in the possibility of picking up a brain lesion of some kind. It is not atypical of tumors of the brain stem to lead to this complete escape from temperature control. At present I have as a patient a child who had a paranatal accident of torsion of the spinal cord. The baby now has a cord bladder, of course, and there is absolutely no temperature control; a single colon bacillus in the bladder sends the temperature soaring to 104 or 105° F. Most paraplegics react similarly. The only optimistic note is that as time goes on the brain seems to give up and the more peripheral mechanisms of heat control come into play.

Conclusion

I should like to close by quoting the last paragraph of a lecture given by Eugene DuBois in 1937; there is little we can add to the final line: "I would like to urge upon clinicians the desirability of thinking of the fundamentals of temperature regulation when they are observing their fever patients. Not only is it a help to better understanding of diagnosis and therapeutics, but it makes even more fascinating that most fascinating of all subjects, the study of disease at the bedside."

Use of Anticoagulants in the Treatment of Coronary Artery Disease

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ALTHOUGH the subject of coronary artery disease is somewhat commonplace, it is one of real concern, for this disease causes an estimated 200,000 deaths annually in the United States. While it is likewise true that the use of anticoagulants in the treatment of coronary artery disease is also somewhat commonplace, there is a certain lack of uniformity of opinion as to which patient should be so treated and which of the many anticoagulants should be used. Hence, I will devote most of this discussion to the anticoagulants themselves.

Effectiveness of Various Anticoagulants

As a result of the research of Charles and Scott, working in Best's laboratory, heparin was recognized in 1936 as the first anticoagulant practical for clinical use. Since heparin is now so well known, I will not discuss its action in detail. The substitutes for heparin, treburon and PARITOL®, were found wanting because of the toxic manifestations that they caused.

Three years after heparin was introduced, Karl Paul Link and his associates made 3,3′-methylenebis (4-hydroxycoumarin) available; it was given to us for clinical trial in the fall of 1940. We made the first report of our clinical experience with the coumarin compound known as DICUMAROL® in February 1941. Although Dicumarol is probably the anticoagulant still most widely employed in the treatment of thromboses, I do not think it is the best of the coumarins. In our own institution, we have used Dicumarol hardly at all in the last three years.

Although we depend on a type of coumarin more than any other anticoagulant, the indandiones are also available. Phenindione is available as HEDULIN® or DANILONE®, and diphenadione, as DIPAXIN®. The indandiones are both potent and effective. Though they are not related to the coumarins, they operate in the same way, i.e., by producing hypoprothrombinemia. However, they have been known to produce toxicity, such as the two cases of agranulocytosis reported by Brown and MacMillan[1] in Toronto. Makous and Vandeveer[2]

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Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

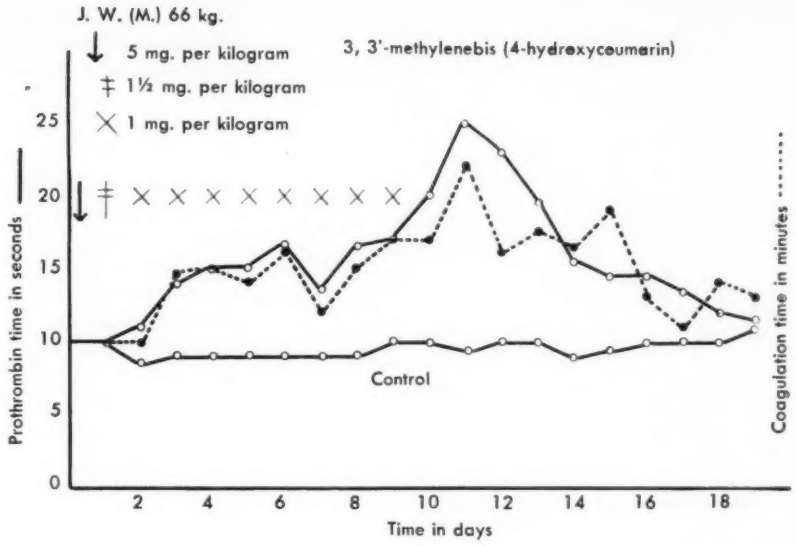

FIGURE 1. Effect of Dicumarol on the prothrombin time and the coagulation time.

also reported a case in which there was hepatitis, anemia, a leukemoid reaction and dermatitis as a result of indandione therapy. Admittedly, such toxic reactions from indandiones are rare; however, since none of these reactions result from administration of any coumarin compound and since I see no significant advantage in using indandiones, I avoid the small hazard of serious complications.

In one of our earlier studies on coumarin administration, we recorded the results in seconds, with the prothrombin of 100 per cent representing a time of 12 seconds, according to the Quick method as modified by Stewart and Pohle. This means that if the prothrombin time is 17 seconds, the prothrombin is 40 per cent of normal; 25 seconds is 20 per cent prothrombin. We still believe that the proper therapeutic range is between 40 and 20 per cent, and we do not believe that there is significant advantage in reducing the prothrombin below 20 per cent. Showing me some petechiae on his face recently, one of our staff men said, "Every time I get below 20 per cent, I begin to get these little hemorrhagic areas. I checked the prothrombin this morning and it was 17 per cent." Since a myocardial infarction two years ago, he has been taking WARFARIN® sodium. Quick demonstrated that bleeding is most likely to result when prothrombin falls below 20 per cent (25 seconds); it is not likely to occur above that level in the normal individual.

Figure 1 is a curve that we made early in our studies, demonstrating prolongation in both the prothrombin time in seconds and the coagulation time (broken line) in minutes. If the coagulation time is done properly, in a water bath at 38° C., this prolongation of coagulation time cannot be demonstrated; only the prolongation in the prothrombin time can be shown, and that is sufficient.

The next anticoagulant that we studied, thinking it might be more advantageous, was cyclocumarol, marketed as CUMOPYRAN®. It was a bit better than Dicumarol, in that we could maintain a steadier level of prothrombin; however, it was never widely used. When Warfarin and Warfarin sodium became available, we lost interest in Cumopyran.

Following the introduction of Cumopyran, ethyl biscoumacetate, known as TROMEXAN®, became available. Figure 2, showing the therapeutic response to Tromexan, is plotted in percentage rather than seconds; admittedly, this exaggerates the curve. This anticoagulant has both advantages and disadvantages. It is advantageous in that it produces an effect

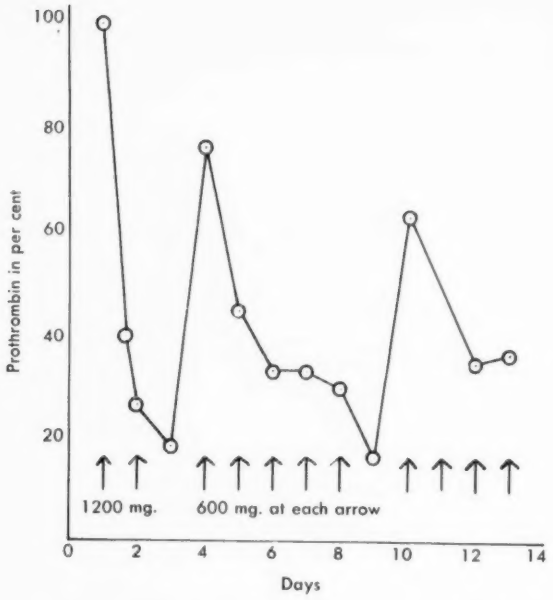

FIGURE 2. The effect of Tromexan on the prothrombin percentage.

within a matter of hours, whereas there is a latent period of 24 hours or more before an effect is demonstrated with Dicumarol. Furthermore, if Tromexan is withdrawn, the effect wears off quickly, which is an advantage if hemorrhagic manifestations develop. However, this effect is negated to some degree now that we have an effective antidote for all of these coumarins. I refer to vitamin K_1 or vitamin K_1 oxide. Vitamin K_1 can be administered orally or intravenously, and, if desired (for example, in anticipation of an operation or if hemorrhagic manifestations develop), it promptly counteracts the effect of any of the coumarins. Vitamin K and blood transfusions are not really good antidotes, and I would strongly urge the use of vitamin K_1 or vitamin K_1 oxide if an antidote is necessary for the hypoprothrombinemia produced by the coumarin anticoagulants or the indandiones.

The disadvantage of Tromexan is in the considerable fluctuation which it produces (figure 2). Soon after the drug is withdrawn, the patient is out of the therapeutic range of 20 to 40 per cent. The fluctuation is so great that some physicians have given Tromexan more than once a day in order to minimize it. For these reasons, I do not like to use Tromexan. However, if a very quick effect in 12 hours or less is necessary, Tromexan is useful, and it may be combined with one of the other coumarin anticoagulants for protracted therapy. I have used it in this way occasionally.

The most recent coumarin substance to be

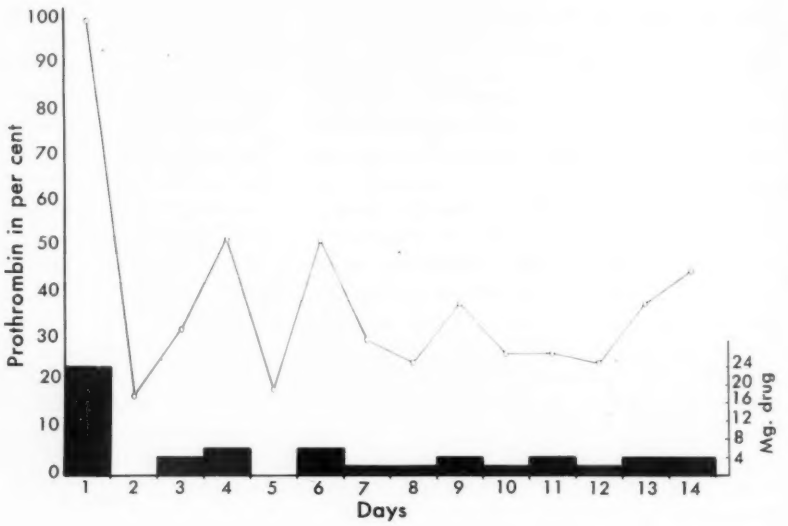

FIGURE 3. Effect of Sintrom on the prothrombin percentage.

made available is SINTROM® (acenocoumarin). It is a very potent anticoagulant and, like Tromexan and Dicumarol, is given orally. I have used it in a few cases. Figure 3, plotted in percentage in order to compare it with figure 2, shows the effect of Sintrom on a patient who was given an initial dose of 24 mg. The subsequent doses were low, in the order of 4 to 6 mg. It is possible to maintain a fairly steady hypoprothrombinemia with this drug; however, although it is effective, it has no great advantage over Dicumarol, and I think that it lacks some of the advantages of Warfarin or Warfarin sodium.

I would like to clarify one point concerning the much-discussed matter of potency, particularly with reference to the indandiones (and they are very potent). For instance, 20 mg. of Dipaxin is the initial dose, with a daily dose of 3 to 4 mg. With Tromexan, which is the least potent anticoagulant, the initial dose is 1500 mg. Any of these doses is tolerated. Since it is not appreciably cheaper to use a small rather than a large amount, I see no significant advantage in using an anticoagulant of greater potency, as long as the drug used is effective.

I started to use both Warfarin and the sodium salt a few years ago. Since I found Warfarin sodium just as effective as Warfarin, I have continued to use only the more soluble Warfarin sodium, which can be given intravenously or intramuscularly.

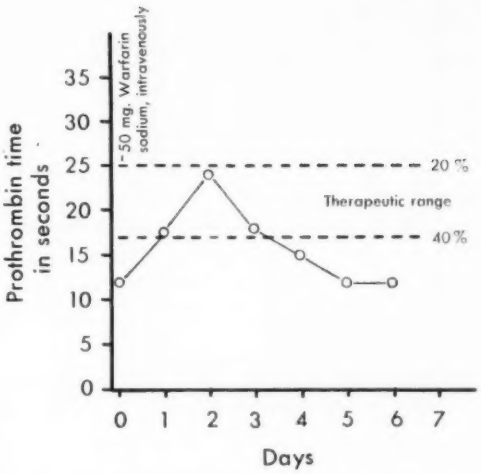

FIGURE 4. Effect of a single intravenous dose of Warfarin sodium on the prothrombin time.

Figure 4 shows the effect of a single dose of Warfarin sodium given intravenously. The effect of a single dose usually lasts for several days, and the prothrombin level does not return to normal until between the fifth and the eighth day. This is also true with Dicumarol. Figure 5 shows the curve obtained when the initial dose of Warfarin was given intravenously and the subsequent doses orally. The prothrombin time is measured in seconds, and the curve demonstrates the regularity with which we can maintain the therapeutic range,

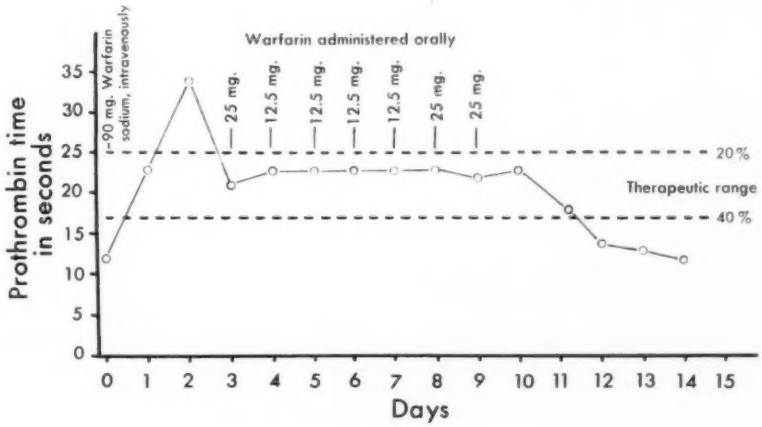

FIGURE 5. Effect of an intravenous dose and repeated oral doses of Warfarin sodium on the prothrombin time.

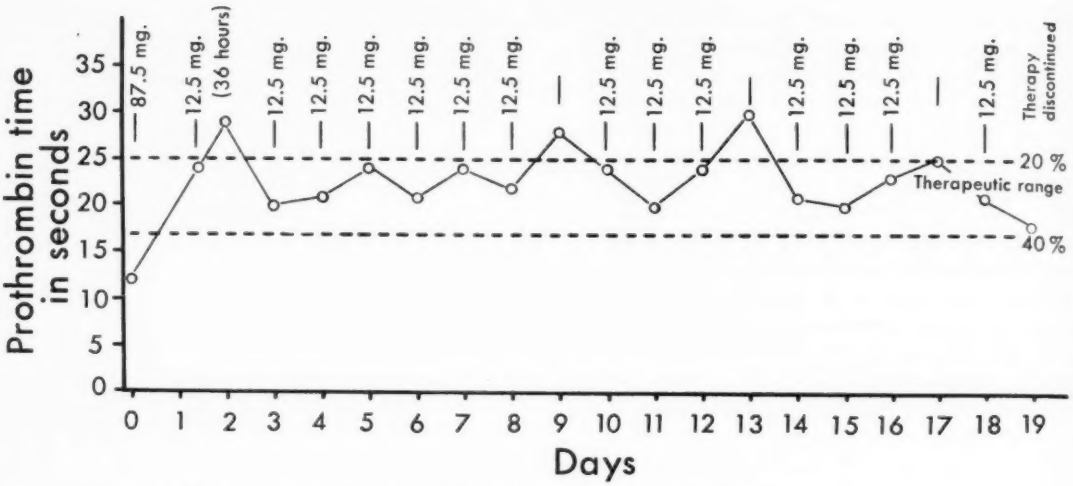

FIGURE 6. Effect of oral administration of Warfarin sodium on the prothrombin time.

which is advantageous. Our house staff now prefers this anticoagulant, because it is less difficult to maintain the 20 to 40 per cent range. Figure 6 demonstrates the effects of the oral administration of Warfarin sodium.

Table 1 shows actual figures of prothrombin for 19 patients after a single injection of Warfarin, demonstrating that the therapeutic range

TABLE 1

EFFECT OF A SINGLE INTRAVENOUS INJECTION OF WARFARIN SODIUM

PATIENT	DOSE (MG.)	LATENT PERIOD (HOURS)	THERAPEUTIC RANGE OF PROTHROMBIN TIME		RETURN TO NORMAL (DAYS)	PEAK EFFECT (DAYS)
			Hours to achieve	*Duration in days*		
1	55	16	20	(2)*	(4)*	2
2	70	8	16	(4)*	(6)*	3
3	70	8	16	2	10	1
4	50	8	20	1	5	2
5	50	14	24	5	9	3
6	50	12†	24	2	5	2
7	75	16	36	4	8	3
8	70	16	36	7	11	3
9	60	16	36	(1)*	(3)*	2
10	90	16†	16	–	–	2
11	90	16†	24	–	–	2
12	60	16†	24	–	–	2
13	85	12†	20	–	–	3
14	85	20	36	–		2
15	75	16†	20	–	–	3
16	75	16†	20	–	–	3
17	70	16†	16	–	–	3
18	75	16†	16	–	–	3
19	45	16†	20	(3)*	(5)*	3

*Figures altered on the basis of patients' having received vitamin K_1.

†Initial prothrombin time not taken at an earlier hour.

–Patients maintained on the oral preparation for variable periods.

TABLE 2

EFFECT OF ORAL ADMINISTRATION OF WARFARIN OR WARFARIN SODIUM

PATIENT	DOSE (MG.)	LATENT PERIOD (HOURS)	THERAPEUTIC RANGE OF PROTHROMBIN TIME	PEAK EFFECT (DAYS)
			Hours to achieve	
1	50	12*	24	2
2	62.5	24*	24	2
3	75	24*	24	3
4	62.5	24*	24	2
5†	75	24*	24	2
6†	87.5	12*	36‡	2
7†	80	14	24	3
8†	80	16	24	3
9†	70	12	16	3
10†	50	20*	20	2
11†	50	20	24	2
12†	95	20*	20	3
13	65	16*	24	3
14†	65	16	24	3

*Initial prothrombin time not taken at an earlier hour.

†Continued on maintenance therapy.

‡Prothrombin time inadvertently not taken at 24 hours.

is achieved in 24 hours or less in most cases. With Dicumarol, the therapeutic range is not reached before 48 to 72 hours; thus, Warfarin treatment achieves the desired effect more quickly. The latent period in Warfarin administration is usually 12 to 16 hours, rather than 24 hours or more. The peak effect is ordinarily obtained between the second and third day. These are real advantages.

Study of the additional cases given in table 2, in which Warfarin or Warfarin sodium was administered orally, reveals that the peak effect and the latent period are similar in both oral administration and intravenous injection of Warfarin. Therefore, there is no advantage in giving the drug intravenously or intramuscularly, unless, of course, a patient cannot take it orally. As far as I know, this is the only coumarin substance which can be given parenterally.

Indications and Contraindications for Anticoagulant Therapy

Regardless of which anticoagulant is used, the indications for anticoagulant therapy are, in the main, those shown in table 3. Although I am going to digress for a moment from my title, I want to emphasize the fourth prophylactic indication, because it is so very important. Not everyone has accepted or recognized this strong indication for anticoagulant therapy. After any major operation or delivery in which there is a history of previous thrombosis, with or without embolism, at least 40 per cent of the patients will have a thrombotic episode the next time they have a delivery or an operation; if ever prophylactic anticoagulant therapy is indicated, it is in such cases.

The usual contraindications to anticoagulant therapy are shown in table 4. I had my "comeuppance" recently when a doctor called

TABLE 3

INDICATIONS FOR ANTICOAGULANT THERAPY

Prophylactically

After

1. Vascular operation
2. Pelvic operation
3. Splenectomy
4. Any major operation in which there is a history of previous thrombosis, with or without embolism

Actively

1. Thrombophlebitis or phlebothrombosis
2. Coronary thrombosis
3. Unquestioned cerebral thrombosis
4. Mesenteric thrombosis, retinal thrombosis, etc.

TABLE 4

CONTRAINDICATIONS TO DICUMAROL THERAPY

Absolute	
1.	Hemorrhagic diseases
2.	Ulcerative lesions
3.	Significant liver disease
4.	Moderate to severe renal disease
5.	Subacute bacterial endocarditis
Relative	
1.	Dietary deficiency states—vitamin K
2.	Fever (?)

me and said, "You have said that subacute bacterial endocarditis is an absolute contraindication to Dicumarol therapy. How about that?" I mention this because, at one time, I treated subacute bacterial endocarditis with Dicumarol and antibiotics (Loewe in New York did the same with heparin and antibiotics), and I found penicillin alone to be as effective. Of course, penicillin does not increase the risk of hemorrhage. Therefore, I believe that Dicumarol is contraindicated rather than indicated in the treatment of subacute bacterial endocarditis. But the questioner raised this point: "If you have a patient who happens to have subacute bacterial endocarditis and then has thrombophlebitis, would you give an anticoagulant?" I would, recognizing that there is some added risk. My point is that you do not give it to treat subacute bacterial endocarditis; however, if thrombophlebitis exists, there is not an absolute contraindication to cautious administration of an anticoagulant.

What causes thrombosis? The three principal factors, alone or in combination, are: (1) damage to the vessel wall; for instance, a blow to the leg, damaging the venous endothelium, or damage from arteriosclerosis, particularly to the coronary arteries; (2) stasis of blood, which may be because of narrowed lumen of the coronary arteries, because of immobility in bed, or because of cardiac decompensation; and (3) hypercoagulability of the blood, which is usually the least important factor.

In coronary artery disease, anticoagulant therapy may well be indicated before a myocardial infarction develops. Patients with angina pectoris often may benefit from such treatment.

Will anticoagulant therapy prevent a coronary thrombosis? Perhaps it will in some instances. However, I have not been as impressed with the prophylaxis of coronary thrombosis as with the prophylaxis of the complications of coronary thrombosis, notably, pulmonary and cerebral emboli.

Anticoagulants in Myocardial Infarction

Why do we give anticoagulants to patients with coronary occlusion who have myocardial infarction? There are four principal reasons: (1) to prevent the extension of the existent thrombus in the coronary artery or the formation of a new thrombus; (2) to prevent a mural thrombus; (3) to prevent a thrombus in the auricle, which is likely if there is auricular fibrillation; and, perhaps as important, although often overlooked, (4) to prevent thrombosis in the extremity vessels, particularly venous thrombosis because of lowered blood pressure and stasis, with the risk of subsequent embolus.

The first to report the use of an anticoagulant in myocardial infarction were Nichol and Page[3] in 1946. Since that time, many have used anticoagulants in the therapy of this condition, and most of the reports have been favorable. There is a difference of opinion, however, as to whether all or only some of the myocardial infarctions should be treated, presuming contraindications are nonexistent.

Russek and Zohman[4] in New York do not treat their mild cases with anticoagulants, because they think the risk with the anticoagulant is greater than the risk of complications. They have recognized that in their series of cases death is much more likely in the severely ill patient than in the mildly ill patient with coronary thrombosis. For instance, in 611 mild cases of Russek and Zohman's series, the mortality was 3.4 per cent; 1.3 per cent of the patients had thrombo-embolic episodes. In 707 of their seriously ill patients, the mortality was 60 per cent, with thrombo-embolic episodes in 11.5 per cent. However, there are many others who believe that virtually all of these patients should be treated with anticoagulants if there are no contraindications, be-

cause the risk of anticoagulant therapy is not great and the advantage is real. For instance, Richter, Del Nunzio and Swiller[5] had a mortality rate of 33.3 per cent in 150 control cases; in the 150 patients treated with Dicumarol, the mortality was 13.3 per cent, a significantly better mortality experience with anticoagulant therapy than without it. I think that, internationally, the general opinion is that the results of anticoagulant therapy are worthwhile and the risk is slight, provided the prothrombin time determinations are dependable.

Method of Treatment

In our institution we start treatment with Warfarin sodium. I have stated that 1.5 mg. per kilogram is the proper dose, but we do not now give a maximal dose greater than 75 mg., whether it is administered intravenously, intramuscularly or orally. If possible, we always give it orally. If the drug is used immediately after operation, as in vascular surgery, the initial dose should not be greater than 50 mg.

The prothrombin time is determined daily, and the ordinary dose thereafter is 0.25 mg. per kilogram or less. We usually have to give between 6.25 and 12.5 mg. each day, omitting the anticoagulant when the prothrombin reaches too low a level, that is, below 20 per cent. We continue this therapy until the patient is freely ambulant or has been discharged.

It is necessary to individualize therapy. No two patients respond exactly alike. There are rare patients who are unduly responsive or resistant to coumarin anticoagulants; therefore, the dose must be modified accordingly. Coumarin anticoagulants can be administered to nursing mothers without hazard of hemorrhage to the infant,[6] but the anticoagulants are dangerous to the fetus in pregnant women. The patient who continues to have angina, decompensation or repeated episodes of myocardial infarction or embolic episodes is best kept on anticoagulant therapy for an indefinite period, provided the prothrombin tests are dependable and the patient can and will cooperate and have prothrombin time determinations at proper intervals. It usually takes two or three weeks of daily prothrombin time determinations to establish the best dosage for this type of patient; then the interval between determinations is lengthened. One physician on our staff has had this regimen for over a year; another has had it for almost two years, and both have prothrombin time determinations at intervals of about one to three weeks. In most patients, it is not difficult to arrive at a schedule in which prothrombin time determinations every two or three weeks are sufficient to maintain them with safety. Some patients, themselves, recognize when the dosage should be reduced, for example, if their gums bleed when they brush their teeth.

Comment

I believe that nearly all patients with coronary occlusion and acute myocardial infarction should have anticoagulant therapy.

In my opinion, Warfarin sodium is the best anticoagulant available today. I usually do not give heparin to patients who have coronary occlusion and acute myocardial infarction, as there is no great urgency for an effect. Since about 35 per cent of these patients have subintimal hemorrhage, heparin administration increases the risk of an excessive hemorrhage. If an effect is obtained 24, 48 or even 72 hours after the occlusion, it should be satisfactory. If the extension of the occlusion is not prevented, at least there is the likelihood of lessening the serious, often fatal complications of pulmonary or cerebral embolus.

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Amenorrhea

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AMENORRHEA is generally defined as the absence of menstruation for at least three months. It is a common gynecologic complaint resulting from causes that may relate to the uterus, ovaries, adrenals, pituitary gland or hypothalamus. When the menarche fails to be established by the seventeenth year, the amenorrhea is called "primary." The term "secondary amenorrhea" refers to the cessation of menses previously present. It is appropriate when dealing with amenorrhea to consider its various causes; the following classification is based largely on that proposed by Sturgis.[1]

One of the most common causes of amenorrhea in the young woman with previously normal menstruation is pregnancy; yet, much to his embarrassment, the physician occasionally will forget this obvious fact.

Rarely, lack of menstruation is due to congenital absence of the uterus or to destruction of the uterine endometrium by extensive sepsis such as tuberculosis. A simple method of establishing the presence of an endometrium capable of response is to administer an estrogen for three weeks, observing whether or not withdrawal bleeding occurs.

The menopause is a classic example of an ovarian cause of amenorrhea. The initial event is failure of ovulation and, later, decrease in estrogen production. As is well known, the periods may cease suddenly or, perhaps more commonly, become irregular or profuse. In women between 40 and 55 years of age, the menopause is a normal event. Occasionally, ovarian failure as reflected by amenorrhea, elevated FSH excretion in the urine, and evidence of estrogen deficiency by vaginal smear may occur in the reproductive years. Substi-

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tutional therapy with estrogen rarely results in resumption of spontaneous menstruation, but it does help in preventing premature atrophic changes in the reproductive tract, the skeletal system and, perhaps, in the cardiovascular system.

Ovarian agenesis or Turner's syndrome, as judged by the number of case reports available, is now recognized rather frequently. In 1938, Turner[2] described the association of sex infantilism, short stature, primary amenorrhea and congenital defects, the most prominent of which were cubitus valgus and webbing of the neck. As gonadotropin assays were introduced and as subsequent patients were subjected to laparotomy, it was shown that urinary excretion of gonadotropins was high and that there was either rudimentary or absent ovarian tissue. It became clear that such patients were afflicted with multiple congenital defects, the most prominent being absent or rudimentary gonads. The lack of secondary sex characteristics was attributed to estrogen deficiency.

Recently, studies of sex chromatin have shown that individuals with ovarian agenesis are usually genetically males.[3] Jost[4] has shown that if the intra-uterine male rabbit is castrated early in the stage of development and then permitted to remain in utero till near expected term, the subsequent genital development will be along female lines. It is postulated that patients with Turner's syndrome may be males who, for obscure reasons, have had testicular destruction early in fetal life and in whom, because of the lack of testes, female genitalia have developed. The term "gonadal dysgenesis" has recently been introduced as a more accurate description of the disorder. Obviously, no purpose is served in informing these patients of the fact that they may be genetically male. Indeed, the whole problem of genetic sex has recently been challenged by the demonstration of three patients with male gametogenesis who showed female-type buccal smears.[5] The problem of genetic sex recently has been reviewed by Witschi, Nelson and Segal.[6] Hoffenberg and Jackson[7] have offered evidence to suggest that the syndrome results from a genetic disturbance rather than from a primary intra-uterine disorder. The cyclic administration of an estrogen to patients with Turner's syndrome, such as 1 mg. stilbestrol daily for 30 days, stopping for seven days and then repeating this cycle indefinitely, usually results in satisfactory development of secondary sex characteristics and periodic withdrawal bleeding. Administration of estrogen should be delayed until it is clear that no further growth will occur. With such therapy, these patients can marry and lead normal lives. Of course, conception is impossible.

The Stein-Leventhal syndrome is a subject of increasing interest. First described in 1935,[8] the syndrome consists of obesity, hirsutism and amenorrhea. The ovaries are large and polycystic and have a thickened capsule. Pathologically, a thick tunica albuginea, follicular cysts and hyperplasia of theca interna are present. Some patients with this disorder may experience irregular or excessive vaginal bleeding.[9] The cause remains unknown, although the theory has been advanced that it may be associated with an increase in secretion of L. H. Recently, it has been shown that in some patients with adrenal hyperplasia, the ovary may resemble that described in the Stein-Leventhal syndrome.[10] Further, it has been found that in some of these patients who also have an increase in 17-ketosteroid excretion, the administration of cortisone results in the return of ovulatory menstruation. In this situation, it has been suggested that there is failure of hydroxylation of the 11 and 21 positions of a C-21 steroid secreted by the adrenal cortex which leads to overproduction of an androgenic steroid, 17-hydroxyprogesterone, instead of the normal production of 17-hydroxycorticosterone.[11] The 17-hydroxyprogesterone is believed incapable of inhibiting ACTH production by the pituitary, resulting in increased secretion of ACTH and further increased secretion of the androgenic steroid. Cortisone acts to inhibit the production of ACTH, removing the stimulus for the hyperplasia. With decrease in production of androgenic steroids, the secretion of pituitary gonadotropins, which has been suppressed by the androgens, returns and menstruation resumes. In those patients with Stein-Leventhal syndrome and an elevated 17-ketosteroid excretion, an attempt to

suppress adrenal overactivity by administering cortisone is the first logical therapeutic approach. In considering treatment for patients without elevation of 17-ketosteroid excretion, a decision must be made as to the advisability of wedge resection of the ovaries.

In many patients, obesity prevents palpation of enlarged ovaries, necessitating culdoscopy or laparotomy to establish the presence of large, pale ovaries. In the patient in whom infertility is the problem and whose husband has been shown to have a normal sperm count, wedge resection appears to be a justifiable therapeutic procedure of considerable benefit. Its rationale remains obscure. It is known that in some women with simple obesity and amenorrhea, weight reduction alone results in return of menstrual function;[12] in a few patients, subsequently shown to have ovaries consistent with the syndrome, weight reduction has been successful. The clinical syndrome remains poorly delineated and not clearly distinguished from simple obesity and amenorrhea. In most instances, in order to avoid needless ovarian surgery, less radical measures such as weight reduction and attempts at estrogen and progesterone substitutional therapy should be tried prior to wedge resection.

It is obvious that pituitary disorders may result in amenorrhea by interference with the production or the release of gonadotropins. The classic example of hypopituitarism in women is Sheehan's syndrome,[13] in which infarct necrosis of the pituitary occurs in association with hemorrhagic accidents of pregnancy. Usually, one can obtain a history of an excessive hemorrhage having occurred at time of delivery which, in many cases, required a transfusion. Following delivery, lactation does not occur, and the patient may complain of fatigue, listlessness and sensitivity to cold. Axillary hair may become sparse, and the pubic hair which has been shaved prior to the delivery fails to regrow. The skin has a peculiar waxy pallor. The reproductive tract presents an atrophic appearance. Laboratory examination will show low excretion of urinary gonadotropins, low excretion of 17-ketosteroids and 17-hydroxycorticosteroids, and evidence of thyroid deficiency. Vaginal smears show evidence of estrogen deficiency. Therapy with cortisone, thyroid and estrogens usually results in a favorable response.

Amenorrhea is frequently the presenting complaint of patients with pituitary tumors or craniopharyngiomas. The amenorrhea may precede by several years the discovery of the pituitary lesion. Therefore, skull films and visual fields are an important part of the diagnostic study of the woman with amenorrhea. Rarely, treatment of the pituitary lesion results in re-establishment of menstruation, so substitutional therapy with estrogen, administered cyclically, is usually desirable in young women.

The Chiari-Frommel syndrome, as originally described, consists of persistent lactation, amenorrhea and uterine atrophy following delivery.[14] The term is also now applied to nulliparous women who have persistent galactorrhea, amenorrhea and varying degrees of atrophy of the reproductive organs. It has been postulated that the syndrome is the result of increased L. H. excretion. In about a third of such patients, pituitary tumors have been found. Treatment in the idiopathic cases is unsatisfactory, but periodic administration of estrogen will produce withdrawal bleeding and partial suppression of lactation.

Amenorrhea is a frequent accompaniment of nutritional disturbances. Although the mechanism is not clear, it has been shown that in starved rats the gonadotropic content of the pituitary is normal or increased but that there is interference with the release of gonadotropins. Clinically, correction of the nutritional disturbance usually results in the return of menses. The mechanism of amenorrhea in anorexia nervosa is more complex and probably initially involves the failure of L. H. secretion due to causes of emotional origin interfering with hypothalamic hypophysial pathways.[15]

Amenorrhea is an integral part of the rare but fascinating syndrome of pseudocyesis. There may be enlargement of the breasts, secretion of milky fluid from the nipple, uterine enlargement, and softening of the cervix, signs that may easily lead to the erroneous diagnosis of pregnancy. Psychologic factors consisting of an intense desire for or a great fear

of pregnancy are usually present. Fried and his co-workers[16] have shown evidence of persistence of corpus luteum function. It is suggested that in pseudocyesis, psychic factors affect the pituitary, presumably by way of the hypothalamus, causing release of L. H., suppression of FSH, and persistence of luteal function, with resultant production of estrogen and progesterone.

Hypothalamic amenorrhea is the most common type of amenorrhea in young women. Also called psychogenic amenorrhea, it is seen in girls going away to school, in nurses entering training, in women separated from husbands or sweethearts (as in time of war), or in association with other forms of emotional stress. Examination of such patients shows little. Vaginal smears usually show evidence of estrogen deficiency. Urinary excretion of FSH is normal, in contrast to ovarian failure where the FSH excretion is high or to pituitary failure where the excretion is low. The normal FSH levels suggest the presence of estrogen, yet about half of such patients fail to have withdrawal bleeding after administration of progesterone. It has been suggested that in this situation, there is failure of release of L.H. from the anterior pituitary with resultant hypoestrogenism.[17] To explain why the lack of estrogen, as evidenced by failure of endometrial response, does not lead to increased production of FSH, it is assumed that the ovary is producing a hormone which is nonestrogenic but which might be a precursor of estrogen and has the ability to inhibit FSH. It has more recently been suggested that in patients in whom progesterone withdrawal bleeding can be induced, estrogen and L. H. have been present to a degree sufficient to provide an endometrial response but not to the extent needed for ovulation.[18]

In the majority of instances, simple reassurance or resolution of an emotional problem coincides with the return of ovulatory menstruation. In some patients, cyclic therapy with estrogen appears to be effective. The amenorrhea may last for a surprising length of time, with menstruation returning after a lapse of several months or even years.

For years, clinicians dealing with problems of menstruation have advocated on empirical grounds the use of thyroid, even in euthyroid subjects. Although there is evidence of a thyroid-gonadal relationship, it remains to be proved that thyroid administration has any effect in the euthyroid individual with amenorrhea. Studies by Buxton and Herrmann[19] indicated that thyroid administration has no effect on amenorrhea or other menstrual abnormalities in euthyroid individuals. Greer[20] has shown that the effect of administered thyroid in normal individuals is to suppress endogenous thyroid function, probably by depression of pituitary secretion of thyrotropin. Such a demonstration renders illogical the use of thyroid in euthyroid individuals. Recently, there has been introduced the concept of the hypometabolic syndrome, of which amenorrhea may be a symptom. It is postulated that the deficiency relates to disturbed physiology of l-tri-iodothyronine at the cellular level. It is suggested that the amenorrhea of the hypometabolic syndrome is relieved by administration of l-tri-iodothyronine;[21] however, further confirmatory studies are necessary.

There is also controversy concerning the use of stimulating doses of x-ray to the ovaries in cases of amenorrhea. This procedure has its enthusiastic supporters, but it has been seriously challenged by geneticists and radiologists. Recently, Arbarbanel[22] showed that "sham" treatment, in which the patients thought they were receiving x-ray but were actually protected by a lead screen, resulted in return of ovulatory menstruation in a significant number of cases. The current publicity concerning the hazards of radiation also has made this type of therapy less attractive. Morgan and Reyes[23] have recently reviewed this problem.

Comment

Amenorrhea is a frequent symptom with many causes, some common and some rare. Appropriate consideration of possible etiologies usually enables one to establish a reasonable diagnosis. The further understanding of the complex mechanism of amenorrhea probably will depend on clarification of hypothalamic hypophysial physiology.

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Too Much 16 Cm. Proctoscopy

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THE selection of a suitable title for a paper is not always easy. Shortly after I began preparing this discussion, a former resident in medicine at Evanston Hospital came to me for investigation of painless bleeding at stool. Since this woman was continuing her residency training at a well-staffed hospital, I was a bit curious as to why she had not consulted someone there. She must have sensed my curiosity, because she volunteered the statement, "I am seeing too much 16 cm. proctoscopy." I seized on this comment as a title which I hoped would arouse some interest.

The doctor had learned that in most patients the 25 cm. sigmoidoscope can be passed for a minimal distance of 24 cm. She might have said, "I am not seeing enough 24 cm. proctosigmoidoscopy." This statement, however, would not have been so provocative.

Proctosigmoidoscopy remains a sadly neglected procedure in physical diagnosis. Reluctance of the patient is undoubtedly a contributing factor, but the chief reason for omitting proctosigmoidoscopy is the tendency of the physician to wait for an "indication." Since the nervous physiology of the terminal intestine is such that neoplasms do not give rise to symptoms early in their course, the only indication for proctosigmoidoscopy is a patient. A more practical statement is that proctosigmoidoscopy is indicated for any patient who is a candidate for thorough physical examination. Certainly no investigation of the gastrointestinal tract is complete without proctosigmoidoscopy. Finally, there is the all too common practice of relying entirely on the radiologist for the diagnosis of rectal and colonic disease. What a shame, when so much can be learned from actually looking into the bowel! This, we must remember, is the first cardinal point of diagnosis—inspection!

How then shall we go about a routine proctosigmoidoscopic examination? Let us consider a plan of procedure which I think will be helpful to both physician and patient.

Instruments

I prefer the Buie sigmoidoscope.† It is 25 cm. in length and 1.5 cm. in diameter. The

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†Electro Surgical Instrument Company, New York.

light source is at the distal end of the instrument. A similar instrument of smaller caliber (1.1 cm.) is available for passage through a contracted anal canal, a narrowed segment of intestine (stricture, obstructing growth), or a tight abdominal stoma. There are other instruments, but, in reality, the type of instrument used is far less important than the manner in which the examining physician uses it.

An essential part of proctoscopic equipment is adequate suction, which serves to evacuate mucus and retained fluids from the bowel, thus facilitating an unobstructed view.

Preparation of Patient

The patient is prepared by means of warm tap water enemas, which are given until the returns are clear. The hospitalized patient can be given a FLEET® enema the evening prior to the day of examination; another Fleet enema is given one hour before examination.

Positions for Examination

The inverted position is the best for this type of examination. It can be accomplished by (1) the patient's assuming the knee-shoulder position, (2) the use of an operating table, or (3) the use of a good proctoscopic table. My chief objection to the knee-shoulder position is that the patient must hold himself in the required position while tolerating the examination. It is not always easy for the patient to cooperate under such circumstances.

In a hospital which does not have a proctoscopic room, an operating table will be satisfactory. The patient is placed on the table in the prone position, with his pubic bone overlying the kidney rest. The kidney rest is then elevated so that the patient's abdomen hangs free. The table is "broken" sufficiently to accentuate the patient's jackknife position and is tilted to depress the head end. This results in an approximation of the inverted position suitable for proctosigmoidoscopy.

I prefer a proctoscopic table which is comfortably padded and which provides for elevation of the patient's pelvis in such a manner that his abdomen hangs free when he is placed in the inverted position. A motor-driven table of this type has now been made available.

The best and most comfortable position for proctosigmoidoscopy for a bedridden patient is the Sims position. The patient can be transported to the proctoscopic room on a flat cart, and the examiner can perform an endoscopic study without moving the patient from the cart. In this way he can have access to all the necessary equipment, especially to the suction apparatus.

Examination

I believe that the success of a proctosigmoidoscopic examination depends far more on the manner in which the physician carries out the procedure than on the equipment used. Although I will not give you a detailed explanation, I do want to emphasize the importance of (1) the explanatory remarks directed to the patient in advance of each step of the procedure, and (2) extreme gentleness in both digital and instrumental manipulations.

External inspection—The first procedure in the examination is the careful inspection of the lower back, the buttocks, the thighs and the anal and perianal tissues, together with gentle laying on of hands.

Palpation—When palpating, the examiner should be especially gentle because of the somatic sensory nerve supply of the anal and perianal integument.

Digital exploration—In digital exploration of the rectum, I like to use the following working classification,[1] which I use in teaching:

"I. Intraluminal (intrarectal)
  A. Impactions
  B. Foreign bodies
II. Intrinsic (mucosal or submucosal, or both)
  A. Inflammatory
    1. Recently injected or thrombosed internal hemorrhoids
    2. Submucosal abscess
    3. Large discrete ulcers, including factitial ulcers
    4. Stricture
      a. Venereal lymphogranuloma
      b. Colitis, especially chronic ulcerative colitis
  B. Traumatic
    1. Enema-tip injuries

2. Impalement injuries

C. Neoplastic
   1. Polyps
   2. Carcinoma

III. Intramural
   A. Endometrial deposits, especially in rectovaginal septum
   B. Benign tumors
      1. Lipoma
      2. Leiomyoma
      3. Fibroma
      4. Neuroma
      5. Hemangioma
   C. Sarcoma
      1. Lymphosarcoma
      2. Fibrosarcoma
      3. Melanosarcoma

IV. Extrinsic (extramural or extrarectal)
   A. Anterior
      1. Prostatic and seminal vesicular enlargement in the male
      2. Progress of first stage of labor
      3. Pelvic masses in the female
      4. Metastases to rectal shelf (cul-de-sac) in both sexes
      5. Pelvic abscess, appendiceal in origin, in both sexes
   B. Lateral
      1. Ischiatic spine and greater sciatic notch (landmarks)
      2. Pelvirectal abscess
      3. Carcinomatous spread into rectal stalks (from prostatic cancer), with resultant narrowing of rectal lumen
   C. Posterior
      1. Coccyx and attached ligaments (landmarks)
      2. Presacral tumors
         a. Inflammatory—retrorectal abscess
         b. Neoplastic
            (1) Teratomas (including dermoid cysts)
            (2) Chromaffin body cysts
            (3) Chordomas
            (4) Sarcomas (soft tissue)
            (5) Metastatic carcinoma
            (6) Tumors arising from bone or periosteum"

Internal inspection (endoscopy)—The proctoscope is inserted gently through the anal canal and is aimed toward the patient's umbilicus. The obturator is then removed, and all further progress of the instrument is accomplished by direct vision—*never blindly*. The instrument is allowed to fall forward or anteriorly, and can usually be advanced to a point directly inferior to the sacral promontory. It must then be levered anteriorly in order to clear the promontory. In addition, it usually passes to the right of the midline. This maneuver necessitates some pull on the mesosigmoid accounting for cramping abdominal discomfort. It is well to warn the patient prior to this maneuver and to assure him that it will do no harm. The patient must be encouraged to breathe steadily and to avoid straining if possible.

I believe that the most difficult part of proctosigmoidoscopy is passing the instrument into the distal sigmoid colon. A pitfall which both the novice and the experienced examiner frequently encounter is the blind pouch. The blind pouch is an apparent dead-end segment of bowel. The novice, however, may be unaware of this condition, or he may not know how to deal with it. The difficulty lies in the examiner's failure to withdraw the proctoscope a short distance in order to obtain a better view. Withdrawal of the instrument for a few centimeters may reveal the curve that was missed or the fold that is hiding the lumen. The fold can usually be moved aside by gently manipulating the tip (distal end) of the instrument. Moving a fold to one side or lifting it may facilitate passage of the tip of the endoscope over a hump (actually another fold) and thence into the lumen of the bowel beyond (proximal). Many of these maneuvers are accomplished by the examiner's using his left wrist in a fulcrumlike action.

Should the examiner succeed in passing the proctoscope the entire distance of 24 cm., and if he sees 2 or 3 cm. more of bowel lumen beyond the tip of the instrument, he has then avoided a blind pouch. However, if he has advanced the proctoscope to full distance but has failed to recognize that the bowel wall is stretched across the tip of the instrument, he

will complete his examination without having seen any of the sigmoid colon proximal to this point. In other words, the examiner has concluded that since the proctoscope has been fully inserted he has accomplished all that can be expected.

An experienced examiner who has passed the endoscope to full distance and has recognized a blind pouch is not content to stop at this point. By levering the distal end of the instrument anteriorly and laterally to the left or right, as dictated by the configuration of the intestine, while simultaneously withdrawing it 2 or 3 cm. to lift the fold which is hiding the lumen, he may succeed in reaching the adjacent segment. At this point he can identify the fold which separates the brightly lighted blind pouch from the darkened segment of sigmoid colon just beyond or proximal to this fold. The expert examiner sometimes uses the suction tip in exerting gentle traction on a fold. In addition, he may resort to manipulating the contents of the false pelvis with his right hand. This is done by palpating the patient's lower abdominal wall while continuing to guide the endoscope with the left hand.

Endoscopic study—Having been concerned thus far with the safe and gentle introduction of the proctoscope, the examiner can next devote his attention to a detailed endoscopic study during the withdrawal of the instrument. Once he has learned the so-called normal appearance of the tissues and the normal variations, he will have little difficulty in determining the presence or absence of an abnormal condition.

During proctoscopy one may see either or both of two physiologic motions which are extrinsic in origin and which are transmitted through the wall of the bowel. One is the pulsation of the right common iliac (or hypogastric?) artery, seen when the distal end of the proctoscope lies immediately to the right of the sacral promontory. The practical significance of this observation pertains to its use as a landmark identifying this segment as the distal sigmoid colon. The pulsation is not seen until the proctoscope has reached a point *proximal* to the rectosigmoid. The other movement is "respiratory," caused by the excursions of the diaphragm, with resultant variation in intra-abdominal pressure and characterized by alternating dilatation and contraction of the bowel.

Within the distal sigmoid colon the examiner can see the concentrically arranged rugae of mucous membrane characteristic of the colon proper. As the tip of the endoscope is withdrawn through the rectosigmoid into the well-distended rectum, the rugae give way to a mucosa which is smooth except for three or four coarse spiral folds known as the rectal valves of Houston. Since it is possible for a rectal valve to hide a lesion from view, it is well for the examiner to "iron out" the rectal valves against the rectal wall. This is accomplished by slowly sweeping the distal end of the proctoscope in clockwise circles while the instrument is being withdrawn through the rectum. This is another maneuver effected by the examiner's wrist.

Just before the tip of the proctoscope is withdrawn from the rectum into the anal canal, the internal hemorrhoidal zone immediately proximal to the dentate margin is thoroughly inspected. Continuing the withdrawal of the instrument through the anal canal the examiner notes hypertrophied anal papillae, anal fissures and other manifestations of anal infection.

Our enthusiasm in encouraging widespread use of proctosigmoidoscopy should be tempered by a constant awareness of the possibility of perforation of the bowel during examination. After introducing the instrument, all maneuvers should be carried out gently and under constant visual guidance—never forcefully and never blindly.

Comment

Not only must we encourage routine proctosigmoidoscopy as a part of all thorough physical examinations, but also we must insist on thorough and adequate proctosigmoidoscopy. The examiner must not be satisfied with 16 cm. proctoscopy.

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1. Nesselrod, J. P.: Clinical Proctology. Philadelphia, W. B. Saunders Company, 1957, pp. 43-45.

The Toxemias of Pregnancy

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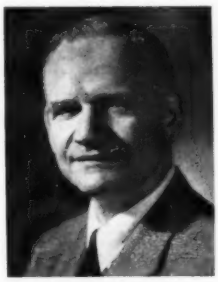

WILLIAM F. MENGERT

It is relatively simple to classify the toxemias of pregnancy. Actually, there are two diseases, acute toxemia of pregnancy and chronic hypertensive vascular disease (table 1). This discussion deals almost entirely with the acute vasospastic diseases known as preeclampsia and eclampsia.

Ophthalmoscopic examination of the eyegrounds is the best method of distinguishing between acute toxemia of pregnancy and chronic hypertensive vascular disease. Figure 1 shows a normal retina. Pregnant patients generally are young women, and those who have hypertensive disease usually have not had it long enough for renal manifestations to appear. They seldom have albuminuria, and often they do not have edema. Therefore, examination of the eyes does not reveal evidence of advanced hypertensive disease but shows quite early disease, namely, the crossing phenomenon and the increased light reflex (figure 2). In acute toxemia of pregnancy, ophthalmoscopic examination shows the typical sausage-shaped vasospasm (figure 3).

Table 2 summarizes my experience with toxemia of pregnancy at the Parkland Hospital in Dallas, Texas, from January 1, 1944 through December 31, 1954. Approximately 10 per cent of the obstetric patients at that charity hospital had hypertension, albuminuria or edema—or, rather, two of those three symptoms—and 0.4 per cent had convulsions.

General Principles

Some time ago, I wrote down the known facts about preeclampsia and eclampsia, and I should like to summarize them.

The acute vasospastic diseases known as preeclampsia and eclampsia affect only the human female. Thus, they occur only in one

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TABLE 1

CLASSIFICATION OF HYPERTENSION IN PREGNANCY

1. Acute toxemia of pregnancy
   a. Preeclampsia
   b. Eclampsia
2. Chronic hypertensive vascular disease
   a. Without superimposed toxemia
   b. With superimposed toxemia

species and only in one sex of that species. They occur only during pregnancy, and only in the second half of pregnancy—usually in the third trimester. Their incidence increases toward term. They may appear soon after delivery, but rarely after 24 or more hours.

Termination of pregnancy cures the diseases. Obviously, therefore, their development depends on pregnancy, on the products of gestation. It depends on the placenta, not the fetus, because the diseases may occur in association with a hydatid mole in the absence of a fetus.

Preeclampsia and eclampsia are diseases of young women, generally less than 20 years of age, although they may affect older women. Principally diseases of the first pregnancy, they may occur in subsequent pregnancies and have been reported in two successive pregnancies, although the latter occurrence is rare. They tend to be diseases of the underprivileged. They have a seasonal incidence, with peaks from February through April and during September and October.

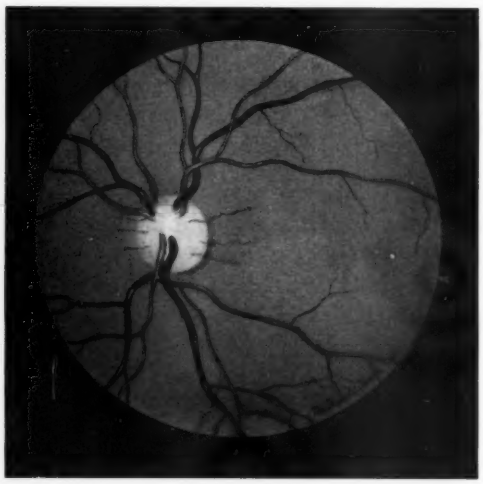

FIGURE 1. Normal. Normally the ratio between retinal artery and vein is approximately 2 to 3.

Physiopathologic Considerations

It is becoming generally recognized that the underlying pathologic process in preeclampsia and eclampsia is acute vasospasm. This acute vasospasm is generalized. When one examines the eye with the ophthalmoscope, one may find that the ratio of the arteriolar caliber is 1 to 3 or even less, instead of the normal of 2 to 3. Curiously enough, in addition to this generally reduced ratio there is also, along the course of a given arteriole, the typical sausagelike spasm. This vasospasm appears sometimes in one area of the body and then in another, and produces the most bizarre manifestations. For example, I know of a patient in whom a piece of the buttock was sloughed off. I know of another patient in whom the lesion was fundamentally in the jejunum, producing necrosis and ultimately resulting in death from perforation of the bowel and peritonitis.

Vasospasm produces ischemia, and ischemia, if long continued or severe, produces tissue damage. It has long been known that the principal focal points of the vasospasm are the brain, liver, heart and kidney. These are the organs where it can be recognized. We recognize it in the kidney, of course, by the production of albuminuria.

Because preeclampsia and eclampsia are acute diseases exhibiting all sorts of manifestations from the mildest involvement to the most severe convulsive toxemia, they tend to be of relatively short duration. Nevertheless, in the milder form vasospasm may last for weeks, and this, we think, will produce tissue damage. We should not allow this to happen.

Management of Preeclampsia and Eclampsia

In the management of acute toxemia of pregnancy, every drug that ever offered the slightest suggestion of promise has been ad-

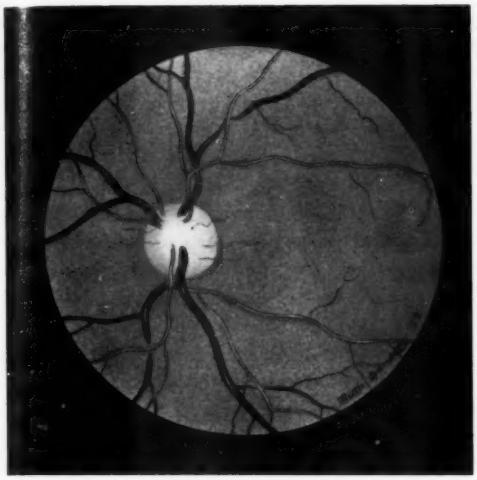

FIGURE 2. Hypertensive disease. The decreased caliber in hypertensive disease results from scarring of the vessel. Thus the wall is scarred and ridged and the caliber decreased. The rigidity of the vessel produces what is known as increased light reflex, appearing as a high light along the course of the vessel. Moreover, the hardness of the vessel tends to flatten a vein wherever the artery crosses a vein. This results in the so-called crossing phenomenon, otherwise known as "nicking."

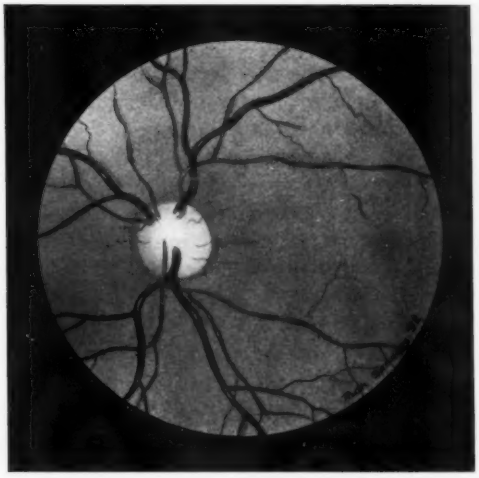

FIGURE 3. Vasospasm of toxemia. Not only is the caliber of the arteriole decreased so that the ratio generally is 1 to 3 or even less, but also individual arterioles exhibit more spasm in one segment than in another segment. This is virtually diagnostic of toxemia of pregnancy.

ministered and every method of treatment has been employed, from denervation of various organs to removal of the renal capsule, sweating, purging, and so on. In other words, if there is a method of management that you want to try, I am sure you can find the proper authority for it. However, only one form of management will cure the condition, and that is termination of the pregnancy.

I wish to emphasize that termination of pregnancy itself may lead to difficulty unless properly conducted. Forcible delivery of a convulsing woman certainly doubles her chances of dying. By forcible delivery I mean manual dilation of the cervix, or cesarean section, or even immediate induction of labor. We must be conservative in regard to the termination of pregnancy; conservatism is the one thing I should like to stress concerning the management of toxemia of pregnancy, be it nonconvulsive or convulsive.

In addition to conservatism in terminating the pregnancy, it is also very wise to have only one physician treat the patient. Generally, what happens is that when a woman seriously ill with toxemia has a convulsion, all the consultants appear. Each has a different idea, and maybe each one carries out his idea, maybe not. It is somewhat like the man who had a cold and who carried a little notebook to write down all the treatments that everybody advised; when somebody suggested something, he would check his book and decide he could get around to trying it by next Wednesday.

I think we must avoid overtreatment of toxemia of pregnancy. Currently, what we do

TABLE 2

TOXEMIA OF PREGNANCY,* PARKLAND HOSPITAL, DALLAS, TEXAS (JANUARY 1, 1944 THROUGH DECEMBER 31, 1954)

Patients discharged	28,088
Patients delivered	23,152
Total cases of toxemia of pregnancy	2,402 (10.4 per cent of patients delivered)
Convulsive toxemia, 88 cases (0.4 per cent)	
Nonconvulsive toxemia, 2,314 cases (10 per cent)	

*Toxemia was diagnosed when a pregnant woman had two of the following signs: hypertension, albuminuria and edema.

first is put the patient to bed, and this is one of the few situations where we advocate total and absolute bed rest. In the horizontal position the spastic vascular tree is considerably relieved. I also think that patients with toxemia of pregnancy should be in the hospital, and unless it is the mildest preeclampsia they should remain there until after delivery.

In addition to bed rest, we prescribe sedation if the patient has moderately severe or severe preeclampsia. Then, after a minimum of two days, preferably three days, we induce labor. This is an induction of necessity, and let us not have any arguments about whether induction is or is not desirable. This is not an elective matter. A patient who has toxemia of pregnancy needs to be delivered because of her disease, so it makes no difference whether the cervix is ripe or not. If necessary, we put a small clamp through it and rupture the membranes, and then we give an oxytocic drug to stimulate pains.

Suppose the patient doesn't "take." Then, within 24 hours, we perform cesarean section. Understand, we do not do this when the patient comes into the hospital with severe preeclampsia or with convulsive toxemia. We put her to bed, give her sedatives, and after three days of conditioning we induce labor. In four out of five such cases, labor will supervene; in the fifth, cesarean section may be necessary after a latent period of 24 hours.

Above all, avoid overloading the patient with fluids. As I have stressed, this is a vasospastic disease. The total capacity of the vascular tree is reduced, and, in addition, if you try to put in too much fluid the spasm will increase. Pulmonary edema is extremely common in these cases. We learned this the hard way a good many years ago. As you know, this disease is often attended by decreased urinary output. One of the men on my staff was very interested in trying to increase the urinary output, and he used diuretics and administered hypertonic fluids intravenously in some profusion. Within a period of nine months we lost five women, three of them directly from pulmonary edema. In the other two cases, pulmonary edema was not primarily the cause of death but was associated with it. So we abandoned the forcing of fluids. If the patient is able to take fluids orally, she takes them that way. If not, she gets them by vein. We give 1500 cc. per 24 hours to replace the insensible losses, plus enough to replace the urinary output of the previous 24 hours. In no instance do we give more than 2500 cc. of fluid in a 24 hour period—and that is the *total* intake of fluid.

I should like to emphasize that this limitation of fluids is not the dehydration treatment that was popular 15 or 20 years ago. Rather, it is a method of controlled and managed fluid intake. Moreover, we do not use hypertonic fluids. Quite a number of years ago, a prominent obstetrician expressed the belief that hepatic damage was the cause of the disease and not the result, and he recommended giving these patients sugar to protect the liver. The practice of giving hypertonic glucose became very widespread in this country, and I am sure that a great many women paid with their lives because of fluid overload.

Table 3 gives some idea of the results with our method of limiting fluid intake. Prior to adoption of the practice of limitation of fluids, more than one of every four of our convulsive patients died. Since then, only 4 of 77 eclamptic women have died. You will be interested to know that we have had a 74 per cent fetal survival rate among 88 eclamptic patients.

What about all the newer drugs that have been introduced and recommended for toxemia of pregnancy, including the hypotensive agents and the diuretics? We contend that this is an *acute* vasospastic disease that develops

TABLE 3

LIMITATION OF FLUIDS IN TOXEMIA OF PREGNANCY
(SUMMARY OF EXPERIENCE TO DECEMBER 31, 1954)

MATERNAL MORTALITY	
Prior to limitation of fluids: 11 eclamptic patients, 3 deaths (27.3 per cent)	
Since adoption of the practice of maintaining fluid balance: 77 eclamptic patients, 4 deaths (5.2 per cent)	
FETAL MORTALITY	
92 babies born to 88 eclamptic patients; 68 survived (74.0 per cent)	

only in pregnancy, and that if we can terminate the pregnancy safely the disease is cured, the blood pressure will come down, and urinary output will increase rapidly. The disease is long-lasting only in its mild form. In the severe preeclamptic or the eclamptic form, the woman either gets well quickly or dies. This is not a long-continued disease, and there is no need to induce a great output of urine when we know from the descriptions of autopsy material that the kidneys are bloodless because the renal arterioles are constricted. Fahr of Germany first described this arteriolar constriction in 1925, and it has been confirmed more recently. Dr. Kark of the University of Illinois is going to discuss renal disease later at this Assembly,* and I am sure he will show you studies of renal biopsies.

Only for very severely ill patients whose blood pressure is around 250 to 300 would I consider the use of hypotensive drugs. Another important symptom so far as treatment is concerned is tachycardia. If the pulse rate rises above 100, and particularly if it gets up to 120, the patient should be digitalized rapidly. We also learned that the hard way.

Cyanosis usually can be combated with oxygen. I see no point, however, in giving oxygen to every eclamptic or severely preeclamptic patient. We give it only to those who are cyanotic.

I have had a rather unique experience in observing the differences between patients with toxemia of pregnancy in the North and those in the South—first in Iowa, then in Dallas, and now in Illinois. There is no question that the kind of toxemia we used to see in Dallas or that Conrad Collins sees in New Orleans is not seen in Illinois and Iowa. Collins, as you know, is the one who talks about tracheotomy in eclampsia. Only in the rarest instance would this be necessary, and then only if you could not oxygenate the patient and prevent gross cyanosis by other means.

I would like to say a word here about labor. In a patient who has severe toxemia, whether convulsive or nonconvulsive, our primary concern is to relieve vasospasm, insofar as possible, by bed rest and sedation. If she is in labor, obviously she has to be delivered, but, if not, we keep her in bed and give her sedation for two or three days. Above all else, we do not attempt to deliver her when she is in the acute, severe phase of the disease.

All patients who have acute vasospastic toxemia of pregnancy should be hospitalized. I do not think it makes any difference how mild the disease seems to be, because severe convulsive seizures can develop rapidly even in mildly preeclamptic patients who have a blood pressure of 145/90 and a trace of albuminuria. I do not believe in ambulatory treatment of this disease. When hypertension, albuminuria and varying degrees of edema develop, the patient must be hospitalized; she must be put to bed. There, if she is conscious and can drink, she should be allowed to take fluids orally, care being exercised to avoid overloading. We would not give her hypertonic fluids intravenously, and under no circumstances would we give more than 2500 cc. of fluid intravenously within a 24 hour period.

We do not use hypotensive drugs in toxemia of pregnancy. We seldom do a tracheotomy in these cases. We do not give the patients diuretics of any kind. We do not digitalize them routinely, and do so only if the pulse rate is rapid. And, above all, a final plea: Treat these patients gently. They are extraordinarily sick. We do not know what causes the initial vasospasm, so it is best to do what we know will get them over the acute episode and then deliver them.

*Kark, Robert M.: Diagnosis and treatment of renal disease. (To be published.)

Diagnosis and Treatment of Constrictive Pericarditis

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C. ROLLINS HANLON

I SHOULD like to make two main points concerning constrictive pericarditis. The first is that the diagnosis is relatively simple if one is conscious of the possibility. Dr. Schwartz† spoke earlier about a high index of suspicion in neurologic diagnosis, and I believe that is the watchword in diagnosis of constrictive pericarditis. If one is conscious of it, the clinical picture is relatively easy to recognize.

The second point I should like to make concerns therapy. In recent years, greater aggressiveness both in early initiation of therapy and in more radical operation has brought about improvement in management of constrictive pericarditis. Both steps have been conducive to better results in this uncommon but important disease. I shall describe two cases which emphasize these points, but first I will run over briefly the characteristic clinical picture of this disease.

Clinical Picture

Chronic constrictive pericarditis usually is seen in a young person, characteristically a young man, who notes the insidious onset of dyspnea on exertion, that is, breathlessness with exercise. The dyspnea is characteristic in that it is unaccompanied by orthopnea; in most instances the patient can lie flat without difficulty. Accompanying this dyspnea is gradual swelling of the abdomen, which on physical examination is found to be associated with enlargement of the liver.

This general picture may go unrecognized for years. Physical examination reveals a small, quiet heart, evidence of ascites, and enlargement of the liver. Usually there is edema of the lower extremities, but not as pronounced

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Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

†Schwartz, Henry G.: Benign tumors of the posterior fossa. Postgrad. Med. 23:410 (April) 1958.

as one might expect with the degree of abdominal enlargement. Sometimes there is edema of the upper extremities, and absence of this finding leads to difficulty in interpreting the edema as cardiac in origin. Instead, one believes that cirrhosis or some other intra-abdominal lesion has given rise to the abdominal enlargement.

To reiterate, on physical examination one generally sees evidence of abdominal swelling and of increased venous pressure in both the upper and lower extremities. The heart is small, or, more precisely, not grossly enlarged. Heart sounds are somewhat distant, and on fluoroscopy the heart is seen to beat less vigorously than normal. The pulse is not necessarily paradoxical—i.e., varying in force with respiration—but sometimes it is; this is characteristic but not essential to diagnosis.

An electrocardiogram usually shows diminution in voltage throughout and depression or inversion of T waves. Special studies such as ballistocardiography and cardiac catheterization usually are not essential to diagnosis.

The "chronic compression triad" of Beck usually can be recognized quite easily: (1) a small, quiet heart, (2) increased venous pressure, and (3) enlargement of the liver and ascites.

This picture has been clearly recognized for over 300 years, and as early as 60 years ago Pick, whose name is associated with this problem, stressed that it might be confused with disease of the liver. As I indicated, this is particularly true when edema of the lower extremities is unaccompanied by edema of the upper extremities. To confuse the picture further, biopsy of the liver may show cirrhosis, particularly if the disease is of long standing; cirrhosis may be secondary to congestion from the cardiac condition.

Report of Cases

Both the patients I shall describe are women, which is not characteristic.

Case 1—This woman was 37 years of age at the time of operation for constrictive pericarditis. Her disease began when she was 23 years of age, so the cause of her symptoms was unrecognized for 14 years. Her first difficulty, in accord with the typical picture already described, was insidious breathlessness and swelling of the abdomen, for which she underwent operation. An ovarian cyst was removed. A year later, laparotomy was performed at another hospital because of abdominal swelling, greater than previously. It was believed that she had cystic recurrence, probably malignant, of the ovarian tumor. At operation, a peculiar sort of cystic change was noted throughout the abdomen. It was not diagnosed specifically at that time and has not been diagnosed to this day. There were diffuse cysts, small and large, throughout the abdomen, with some enlargement of the liver.

Subsequently, she was readmitted to the hospital because of edema of the lower extremities, which was diagnosed as thrombophlebitis. She was admitted again after seven years of symptoms with what was thought to be angioneurotic edema, because by this time she had edema all over. Three years later a diagnosis of cirrhosis was made on the basis of a biopsy of the liver—and indeed she did have cirrhosis secondary to chronic cardiac compression.

We saw her early in 1957, at which time an alert assistant resident, thinking of the possibility of constrictive pericarditis (and considering the possibility was all that was necessary), examined her chest x-ray (figure 1). Although it was not especially characteristic of the total encasement type of constrictive pericarditis that one often sees, he did observe calcification over the left auricle, patchy calcification running over the right auricle, and also a band of calcium down toward the diaphragm.

Cardiac catheterization, which, as I stressed before, is not always necessary, was done, and showed two things, pulmonary artery hypertension and a characteristic diastolic pattern (figure 2). The pulmonary artery tracing showed an increase in pulmonary pressure, a pulmonary hypertension of about 40 to 45 mm. Hg, and in the right ventricle the systolic pressure was elevated to the same level as the pulmonary artery and the base line was elevated in diastole. This is characteristic and reflects the physiologic change in this disease,

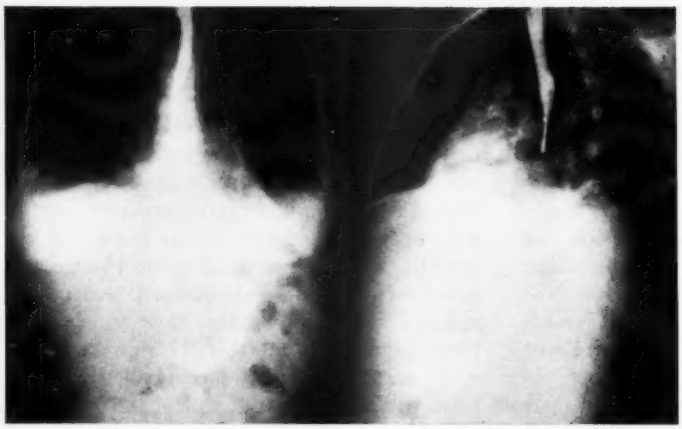

FIGURE 1 (case 1). Roentgenogram showing patchy calcification over right auricle and left auricle, the latter running down as a band which is attached to the diaphragm.

in which ventricular diastolic filling is impeded. There was a characteristic sharp downward dip in early diastole, which rose promptly to a plateau at about 20 to 25 mm. Hg. Of course, diastolic pressure normally should be zero in the right ventricle, and the elevated base line is quite characteristic of impaired diastolic relaxation. I will not dwell further on the tracing except to comment that it was believed to be consistent with chronic constrictive pericarditis.

The patient had had an inflammatory episode related to the chest which was compatible with tuberculosis. It was noted at operation that the pericardium was thick, heavy and calcified, as is typical after tuberculous infection. This was removed by way of a bilateral anterior thoracotomy. The operation was un-

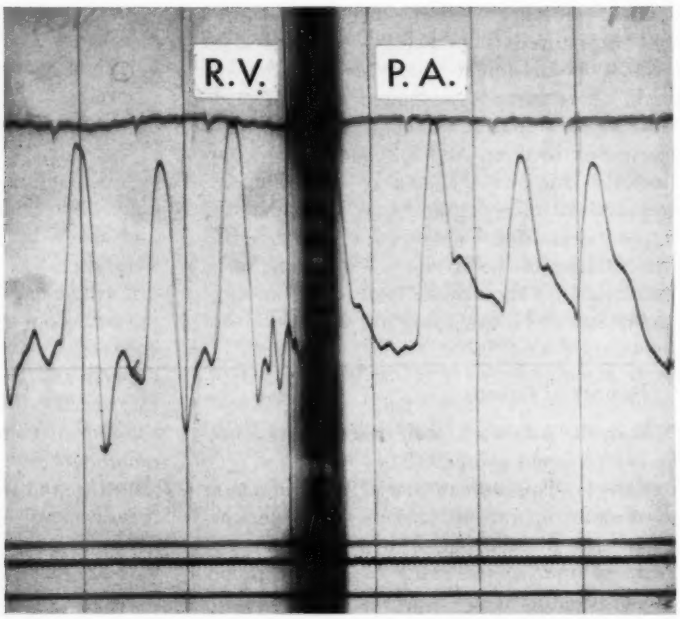

FIGURE 2 (case 1). Pressure tracing from catheterization of right side of heart. In the ventricular tracing (R.V.) the early diastolic dip below the base line and the general elevation of base line in diastole are characteristic.

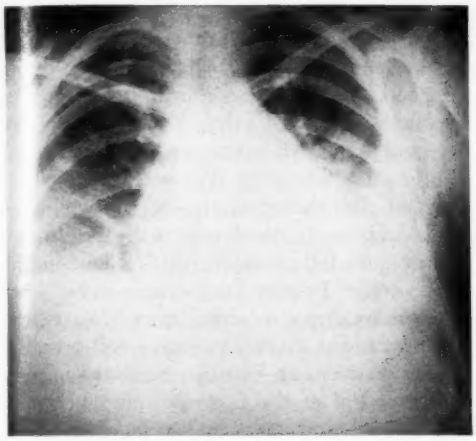

FIGURE 3 (case 1). Bedside roentgenogram showing cardiac enlargement on first day after operation.

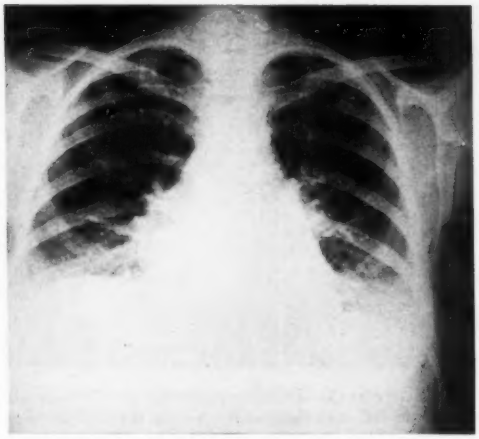

FIGURE 4 (case 1). Roentgenogram of chest several weeks after decortication of the heart. Result good; heart larger due to better diastolic filling.

eventful and the clinical result was good. The pressure in the venous system fell promptly after operation, and symptomatically the patient was much better. She represents an uncomplicated and satisfactory therapeutic experience after a complex diagnostic problem.

A bedside roentgenogram made the day after operation showed considerable enlargement of the cardiac shadow (figure 3). This enlargement is understandable when one considers that the heart had been under compression for many years. The myocardium was atrophic, and when the dissection was begun over the left ventricle, as is customary, after a section of about 3 to 5 cm. had been removed, the soft myocardium began to herniate out through the pericardial opening in mushroom fashion. It almost flowed out like JELL-O®, and when complete pericardial removal had been accomplished the heart was obviously one-third to one-half larger. Although it was pulsating through a larger area of excursion, it still gave one the impression of a weak, flabby heart.

It is customary not to give digitalis before operation, but it is advisable to give it postoperatively because one of the feared complications of an otherwise successful procedure is cardiac failure. In some cases this has been attributed to sudden strain on a previously splinted myocardium which is unsupported in the postoperative period and thus may go on to failure. On the other hand, many such failures in the past may have been due to inadequate decortication.

A roentgenogram made several weeks after operation (figure 4) showed some residual fibrosis at the left base, and the heart still was larger than before operation. This was not a deterioration but rather was an improvement, I would say, associated with increased diastolic filling. The patient's clinical state has been very gratifying in the 10 or 11 months since operation.

Case 2—The second patient was older, 48 years of age, at the time of treatment. There was no special diagnostic problem but the case represented an interesting therapeutic problem at operation. We may review some aspects of the diagnosis in connection with the initial chest roentgenogram (figure 5), which was perhaps a little more characteristic. There was calcification running down over the right and also over the left ventricle. In the oblique view, one could see a complete rim of calcification along the diaphragmatic surface of the heart.

The patient had been ill for five years with rather characteristic symptoms and signs. Venous pressure was 225 mm. of water. The

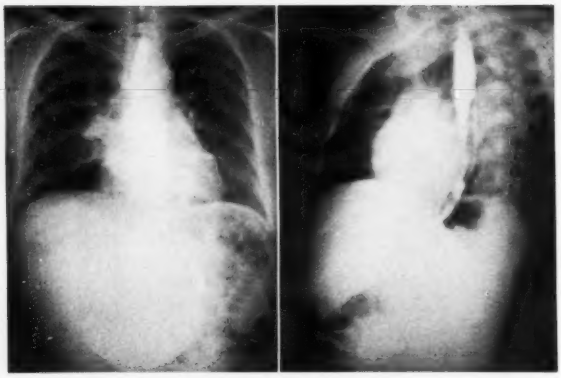

FIGURE 5 (case 2). Initial roentgenogram showing calcium over left and right ventricles. In the oblique view there is calcium extending down over the diaphragmatic surface of the heart.

only confusing aspect of the clinical course prior to the diagnosis of constrictive pericarditis was the fact that she had been apathetic and tired and had a low basal metabolic rate with some swelling of the upper extremities. This was thought to be due to hypothyroidism and she had been receiving thyroid medication. Another physician made the diagnosis of pericarditis, and surgical treatment was carried out as in case 1, through a bilateral anterior thoracotomy.

As for the surgical technic, we recently have used bilateral anterior thoracotomy in contrast to an extensive left thoracotomy or a median sternotomy. I emphasize this point because wide exposure may be vital to thorough decortication. All three of these approaches may give such exposure.

We did what we thought was an extensive removal of the calcific pericardium, and after we had accomplished this by a long and tedious dissection we were disturbed to find that the venous pressure, measured directly in the right auricle, still was 25 cm. of water. It seemed that the decortication had been adequate, and the only thing that remained was some of the diaphragmatic plaque joined by a rather narrow band of fibrous tissue to the heart in the region of the interatrial groove. This hardly seemed sufficient to explain the residual increased pressure in the right auricle. We therefore put a finger in the right auricle to rule out the possibility of an obstructing clot or some tricuspid stenosis. There was no clot, and both venae cavae were widely open, as was the tricuspid valve. We closed the auricle and proceeded to remove the fibrous band mentioned previously. We were gratified to find that after the relatively simple division of this band from its attachment to the diaphragm the pressure fell promptly to 8/2 cm. in the right auricle. I stress this because many poor results have been recorded even after extensive operations in which some small residual calcific encasement remains. Such tissue may appear trivial at the first operation but may well be the most frequent cause of poor results that have been attributed to various factors, such as myocardial difficulty, secondary change due to intramyocardial fibrosis, and so on. This operation demonstrated clearly that one must be extremely careful to remove all of the constricting pericardial encasement.

In addition to the two main points I have stressed, namely, alertness to the diagnostic possibility and aggressive and thorough operative therapy of constrictive pericarditis, there are some additional points, perhaps minor, that I might dwell on.

A roentgenogram of the chest of the patient in case 2 made some months after operation (figure 6) showed that she still had calcium along the diaphragm, with possibly a little residual over the left auricle. There was one additional finding at operation in this case. In the atrioventricular groove we encountered a caseous, grumose mass whose dissection released about 2 cc. of creamy pus. Culture of this material and inoculation of guinea pigs were done, and although it was our strong conviction that it represented tuberculous pus, we were never able to prove this.

The etiology of her disease is uncertain. It is our impression that it probably was tuberculous. I mentioned the creamy pus to bring out two points about operative therapy. I said it could be done earlier in the course of the illness and that it should be more aggressive. By earlier I mean that if a patient has an acute tuberculous effusion with evidence of cardiac constriction one should not operate

immediately but should employ supportive and antibiotic therapy, usually combined with aspiration of the pericardial sac. If symptoms recede, one may not have to operate. However, classic chronic constrictive pericarditis may develop in a relatively short time, sometimes within a year after the onset of acute symptoms and pericardial effusion. In previous years, under such circumstances one would have been apprehensive about whether or not the active tuberculous process had burned itself out and would have hesitated to operate for fear of spreading the disease. With specific antituberculosis chemotherapy this is no longer a problem. In the second case I described, the patient was given antibiotic coverage before operation in anticipation of possible activity of the tuberculous process. The relatively benign course, despite contamination with pus (although we could not prove this was tuberculous), possibly may have been associated with this tuberculostatic regimen. This permits us to be more aggressive and allows relatively safe operation early, before late chronic changes such as cirrhosis and other changes in parenchymal organs occur. I must stress, however, that although one may operate early, not every patient with a simple pericardial effusion, even if it is tuberculous, requires operation.

We begin the dissection over the left ventricle. In explaining the physiologic changes found in these cases, we feel that constriction of the left ventricle is important and constriction of the right ventricle is important, rather than constriction of the venae cavae. Constriction of the right auricle and vena cava will not increase pressure in the pulmonary artery. In other words, interference is all on the proximal side of the pulmonary artery and there is no reason why the pulmonary artery pressure should increase. Therefore, from the physiologic standpoint, lack of expansion and filling of the left ventricle is an important factor, and difficulty in filling the left ventricle may give rise to pulmonary hypertension, which is present rather characteristically in constrictive pericarditis.

It is important to decorticate the left ventricle and to do it first, because if one decorticates the right ventricle first and allows increased filling, driving more blood into the lungs before the left ventricle can accept it, disastrous pulmonary edema may ensue due to failure of the left ventricle to propel the amount of blood given to it.

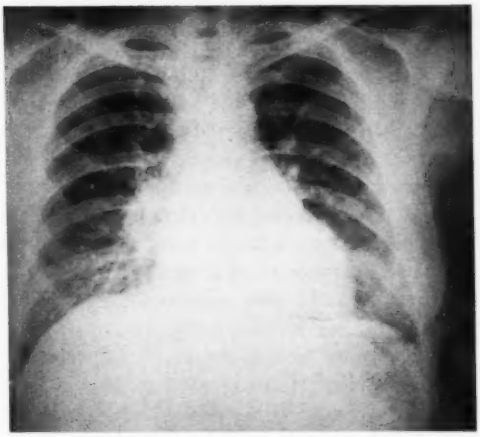

FIGURE 6 (case 2). Roentgenogram several months after decortication of heart with good result. Calcium remaining over left auricle is not impairing cardiac function.

These are technical points, of considerable theoretical importance and also of practical surgical importance, but what I would like to stress are the two points I made at the outset of this discussion. The first was diagnostic and the second was therapeutic. The diagnostic point is that one must be conscious of the possibility that constrictive pericarditis may exist in any young person who has symptoms suggesting heart-failure but without the characteristic background of valvular disease or hypertension. One must also suspect it in cases which masquerade as disease of the liver. Indeed, the latter may be present secondarily, so a high index of suspicion is essential. The therapeutic point is that one should not delay surgical treatment indefinitely for fear of exacerbating tuberculosis, if tuberculosis is the cause, but should aggressively pursue the surgical treatment of this disease. When operation is done, it should be thorough, meticulous and complete. Under these circumstances the management of this somewhat uncommon but still very important disease will be attended by much better results than have been attained in the past.

Home Care and the Practitioner

E. M. BLUESTONE*

Montefiore Hospital, New York

E. M. BLUESTONE

CARE has been provided for the sick in their homes since the earliest days of recorded history. It is, in fact, the original form of care which was offered in conformity with medical knowledge existing at the time. The motives which later prompted the idea of collective care in institutions situated at a distance from the patient's home must obviously have been based on two kinds of pressure: (1) the inadequacy of the home under certain conditions of illness (and of the health of those who surrounded the ill person) and (2) the necessity for transfer elsewhere in the best interests of the patient and those who were exposed to him. The earliest of all hospitals, the leper hospital, illustrates the point, as it shows how society protected the sick individual, as well as itself, against illness and all its medical and social consequences. If, in the case of the pesthouse, society benefited more than the sick man, it was only because primitive men were handicapped in a variety of ways which sooner or later yielded to progress. The more men gained in knowledge the more they learned, up to our own time when the tempo of invention and discovery is startlingly rapid. The microscope is still far ahead of social response as one of the symbols of latter-day hesitation. Home care as we know it today is part of that response.

Having paid our respects to our ancestors, who did the best they could with the materials at hand, we can now contemplate the latest community resource, which has been developed in our generation for the first time, and evaluate it from the point of view of each person concerned. The reorganization of the modern general hospital to provide for an inte-

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grated and indivisible combination of intramural and extramural care (the former within the hospital and the latter within the sick person's home, or substitute for his home) on a continuing basis, with free movement in both directions as required, is without precedent. It is based on the age-old necessity of individualizing the patient's care as a means to his cure or relief. We find this principle, although not this method, restated throughout history, regardless of the status of medical science at the time. It was applied by the members of the faculty of the medical school of the University of Louvain 500 years ago, when they taught medicine in the homes of patients as well as in St. Peter's Hospital.

The Boston Dispensary reiterated the ancient principle in 1796, but it had no hospital beds to carry it out. At that time there was no public hospital other than the Pest House in Boston, "so that needy patients had perforce to be treated in their homes." Florence Nightingale, who was as effective in administration as she was in nursing, again drew attention to the principle in the middle of the last century in a statement which bears repetition: "Hospitals are at best only a necessary evil; a necessity in an intermediate state of civilization. I suppose that everyone will agree with me that every sick man is better off at home if only he could have the same medical treatment and nursing that he would have in the hospital." Over the ages, these motivations have brought us closer to realization of this principle in our time because of the far greater availability of social and medical resources which, if desired, can be marshaled, harnessed and exploited for this purpose. They explain the development of home care in its modern version, and they must be invoked in writing its history. We review them here by way of explanation, in connection with the first hospital program of its kind, which started its successful career as a demonstration project at Montefiore Hospital in New York on January 1, 1947.

The hospital-home care program was the climactic result of a number of adjustments to the new teachings of modern medicine and sociology, these being viewed stereoscopically and applied as a unit. As we emerged from the 1920s at Montefiore Hospital, we became more firmly convinced than ever that in this "hospital for chronic disease" we were in fortunate possession of a prize laboratory for a study of medical-social combinations of all kinds. The hospital was started in 1884 as a custodial institution and, learning from experience, we anticipated medical science somewhat by the construction of a modern general hospital in 1914 on Gun Hill Road which was built to accept the changes of later years. It had all the traditional characteristics of the general hospital for acute illness, although it was limited to chronic illness in its wards. This exhibition of foresight gave our generation an opportunity to deal with functional matters in a structure that was sufficiently flexible and adjustable to changing needs.

Basic Principles

In 1930 I propounded the principle of integration for treatment of acute and chronic illness (which we subsequently publicized as prolonged illness) in the general hospital, so long as either type of patient required a hospital bed. This called for eliminating duration of illness as a criterion for admission or retention in a hospital and substituted the criterion of specific, essential need. From the beginning this hospital has been, and continues to be, a rare voluntary general hospital of its kind and scientific quality. Its very uniqueness proved the importance of the principle of integration and continuity of care. With its high grade of facilities it has been teaching a lesson which, when applied, relieves, to that extent, the burden created by the process of transferring patients in midstream ("dumping" them).

Admission Criteria

The next logical step in organization was planned over the decade of the 1930s and was handicapped by mistaken financial arguments as well as by a hesitant medical profession. It was an answer to the question posed by the applicant—acutely or chronically ill—who did not require a hospital bed but who nevertheless was being admitted or retained more for

social than for medical reasons. Poverty and homelessness, in varying degrees, were too often the controlling elements in the decision. Under the best of hospital circumstances, we learned that collective service inside such institutions militated against the idea of individualization of care and that it was, in large measure, impersonal, mechanical, somewhat chilly and even deadly in its routines. The kind of care that we were seeking, while breaking down the barriers artificially set up between acute and chronic illness, seemed to us an eternal challenge to hospital authority, which had taken on a grave responsibility when it consented to the transfer of the patient from his home into the hospital. Individualization is difficult to realize when sick people are herded in large numbers and exposed to each other directly and indirectly. It must be added that a sound extramural hospital program of home care is one way of teaching lessons in individualization which can be carried over into the intramural aspects of the hospital's work.

Extramural Home Care

Hospitals should be offered to the sick as a matter of necessity rather than of choice. With such thoughts in mind, we set up an extramural home care service to round out the service rendered intramurally. The bed outside the hospital walls was as much under the hospital's jurisdiction as the bed inside, and only the location distinguished one from the other. The pattern of continuous care in either or both places, regardless of duration or curability of the illness, was integrated to the point of indivisibility. We were interested in the whole patient as a psychosomatic individual who had to be relieved of the burden of overcoming the handicaps of time and distance in addition to the handicaps of his illness. Total integration of service pointed out the way. Such controlling factors as social and medical urgency were evaluated and compared. We knew that medical urgency was greater in the case of the intramural patient and that social urgency was greater in the case of the extramural patient, while each partook of some of the characteristics of the other. Concentration of service on both sides of the hospital wall had to be adjusted to such requirements. Knowing that society somehow manages to respond with reasonable promptness to acute situations, just as individuals do to each other in time of crisis, we felt the obligation to provide for those who were still suffering from what might be called "blunted acuteness." Some patients do not heal or heal slowly, and, their problem being stubborn and tenacious, the response must be equally stubborn and tenacious. We declined to admit a prognosis of incurability and held that such problems must be kept before our eyes until they are solved by either God or man.

In all instances the bed, whether located within the hospital, the home, or a substitute for the home, was placed under the supervision of the best medical authority available, and the patient's problem was dealt with unbrokenly in the best traditions of the scientific laboratory. The advantages of this kind of home care to the patient cannot be overstated. The hospital which offers such a program of service redeems itself while justifying its high place in the medical life of any community. It is an indication that the challenge has been accepted and that hospital facilities will be available to the patient *and to his physician* intramurally and extramurally wherever and whenever they are required. With such distribution of hospital service, the social worker (or her equivalent) has, at last, an adequate resource for the care of rejected patients, and finds herself consulted more frequently by the medical staff on such a vital factor as the environment in which the patient's illness was incubated.

The pattern of medical care in home and hospital, singly, continuously or alternatively, is on high logical and moral ground if only because of its humaneness. Clinical waste is minimized while opportunity beckons. There are important by-products of this combined program of service, such as improved hospital bed turnover, more intensive use of such beds, and reduced over-all costs for medical care to the community as a whole, but the original motivation for the home care program outlined here must dominate its administration. Medical education and research, in their en-

vironmental as well as strictly scientific aspects, are more readily promoted in a continuous plan of service which does not depend on such criteria as duration of illness, curability, financial eligibility and the like.

The General Practitioner's Role

From this brief outline of the modern hospital-home care program it must be clear that one of the acid tests of its success—apart from its therapeutic values in terms of life and comfort, its power of discriminate distribution of service, its individualization of care, its economies in money and in hospital beds and other benefits—is its ability to absorb the general practitioner and make him part of the medical team, exposing him at all times to the educational opportunities of the hospital. It brings needed hospital facilities to him and his patient freely in every instance where it is not absolutely necessary to reverse the process and transport the sick person to the place where the facilities are located. If a patient can be cared for in his home safely and comfortably, with help given to him and to his physician as required, this should be the method of choice whether or not he can afford this extra service. The early fears and suspicions that this kind of home care might somehow overlook the general practitioner, pass him by, or injure his status have been dispelled by successful experience with this program. The hospital staff physician is less likely to look down on the practitioner in the presence of a home care program of which both take advantage and which increases the respect of each for the other. As a means of breaking down the barriers of the "closed hospital" this method is without equal! Apart from any other consideration, a home care program is quite a stimulus to medical economics, in which the practitioner is the gainer.

I submit that the way to solve a number of organizational problems in medical life on both sides of the hospital wall, and to reduce cleavages, is not by perpetuating the obstacles to reunion on a productive basis but by removing them through the friendly, helpful and beneficial characteristics of an integrated home care program in which the hospital accepts leadership—as it does when more difficult medical problems arise in any community. The extramural practitioner has a vital contribution to make, and it is no less important than that made by the intramural specialist. Hospital walls should therefore be looked on as architectural conveniences rather than as barriers to progress.

The future of medical care is involved in improved relationships like these, and they are, therefore, the legitimate and highly moral concern of organized medicine. Hospital-home collaboration must be tested by its power to increase the practitioner's usefulness and raise his standards to ever higher levels. This will be possible when the practitioner's hospital education will be planned in accordance with the principles recommended here.

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1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Indications for Heart Surgery

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The gathering of data necessary to determine the operability of individual cardiac lesions requires the teamwork of the cardiologist, physiologist and the surgeon. The final decision in each case depends on a balance between the prognosis without surgery and the risk involved in the operative procedure. The risk of surgery must also be considered in the light of the completeness of normal function which may be expected from the procedure if it is successful. All of these factors except the prognosis without surgery are changing rapidly. The indications for specific lesions of both congenital and acquired origin will be discussed in the light of present technical attainment, and some predictions for the immediate future will be made.

SYMPOSIUM

Proper Selection of Cases for Heart Surgery

HENRY SWAN* AND S. GILBERT BLOUNT, JR.†

University of Colorado School of Medicine, Denver

DR. HENRY SWAN: In a discussion of the selection of cases for any surgical procedure, it is, of course, appropriate to ask a surgeon to participate. Certainly the criteria for selection depend on the procedure itself, that is, the risks of the operation and the results. Further, the diagnosis of the patient's condition and his management before and after operation are the surgeon's responsibility. I wondered, therefore, why my colleague Dr. Blount, an internist, was asked to take part in the discussion, until earlier this evening I overheard someone ask what he did. He replied, "I tell Dr. Swan what to do at the operation." I think certainly that is an adequate reason for including him. Also, the results of any surgical procedure should never be reported by the surgeon. They should be given by an objective observer. In this way they are not colored by the hopes and aspirations of the surgeon who performed the operations.

HENRY SWAN

S. GILBERT BLOUNT, JR.

It is our purpose to present some data as obtained by Blount on patients who were operated on by Swan. We have been able to gather an impression of the merits of various procedures and thus to delineate better the methods of selecting patients for operation.

Obviously we cannot cover the entire field of heart surgery in the brief time allotted, and we have therefore selected a few types of car-

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Presented before the forty-second annual Assembly of the Interstate Postgraduate Medical Association at Chicago.

TABLE 1

PROGRESSIVE INCIDENCE OF SIGNIFICANT CARDIAC ARRHYTHMIAS IN 280 CASES OF HYPOTHERMIA

	FIBRILLATION	DEATHS	STANDSTILL	DEATHS
First 100 cases	15	12	7	1
Second 100 cases	8	4	1	1
Last 80 cases	3	1	0	0

diac disease to discuss. Dr. Blount will present the points he considers important in regard to diagnosis and differential diagnosis and preoperative evaluation. Then I will discuss briefly the technical aspects of the procedure, after which Dr. Blount will give our results and the objective findings after operation.

As we talk about the selection of patients you will see how the results have influenced our thinking in this respect. (I am sure Dr. Blount will tell you that any improvement in mortality figures is entirely the result of better selection of patients on his part.)

Before we discuss the various types of cardiac disease, I would like to mention some changes in technic in open heart surgery that we have found helpful.

Hypothermia

First let us consider the technic of hypothermia as a method for approaching the open heart. We still use the rather simple method of immersing the patient in cold water and then adding ice until it is quite cold. We use diathermy wrapped around the pelvis so the patient can be warmed during the operation. The patient leaves the table with a relatively normal temperature. Various physiologic aspects of the patient's circulation are monitored, and we have a defibrillating machine at hand. Most important perhaps is the anesthetist's respiratory bag with which he maintains constant adequate oxygenation by good artificial respiration.

At present we feel that the risk of hypothermia as we use it is essentially zero. This is quite a change in position for me, because I have always worried about the intrinsic risks of hypothermia. Having gradually limited its use and applied certain physiologic principles to its management, I think it quite fair to state that the risk of the technic itself is very close to zero, if one stays within its limitations.

Some of the points we consider important are as follows: not lowering the temperature too much (30 to 32° C.); external surface cooling to cool the periphery of the body before the central organs (we warm in the opposite direction); hyperventilation to maintain a persistent respiratory alkalosis, which has a direct effect on the irritability of the heart; intravenous glucose for the same reason; fresh blood in plastic bags to avoid the bleeding tendency; an adequate incision which exposes all aspects of the heart so one can cope with any situation which might arise; very careful positioning of the patient, which is crucial in avoiding coronary embolism; slowing of the heart with neostigmine, which reduces its metabolic needs and irritability; clamping the aortic base, which is another way of saying occluding the coronary artery ostium to protect from air embolism; and, a very important point, not employing the technic of hypothermia with a circulatory occlusion to exceed six minutes. One can repeat it two or three times and actually obtain 10 to 14 minutes of operating time within the heart, provided one divides the time into episodes. A final important point is rewarming with diathermy, which warms the important internal viscera before the periphery.

The principal complications of hypothermia in our experience have been cardiac arrhythmias, specifically ventricular fibrillation and standstill, and the effect of the lowered temperature on the clotting mechanism. Table 1 gives the incidence of significant cardiac arrhythmias in 280 cases in which hypothermia was used. You can see the progressive diminu-

TABLE 2

PROGRESSIVE INCIDENCE OF CLOTTING DISTURBANCES DURING OR AFTER HYPOTHERMIA (280 CASES)

	BLEEDING	THROMBOSIS	DEATHS
First 100 cases	4	2	6
Second 100 cases	3	2	5
Last 80 cases	2	1	0

tion in their incidence. The effect of hypothermia on the clotting mechanism involves a bleeding tendency during operation and an excess tendency to thrombosis afterward. There has been a progressive diminution in the incidence of both tendencies (table 2).

The actual operative risk of open heart procedures during hypothermia is shown in table 3. When this table was prepared, we had performed open heart procedures during hypothermia on 192 patients, with, as you can see, progressive improvement in the mortality rate. I think it is impossible to get the mortality risk below a certain point with a bilateral thoracotomy and open mediastinotomy and an opened heart in a patient who has a sick heart to begin with. Obviously there is an intrinsic risk in the operative procedure itself, irrespective of the method.

Cardiac Bypass and Pump Oxygenators

Sometimes a longer period of operating time is necessary than hypothermia can safely provide, and at present there is a great deal of interest in cardiac bypass using pump oxygenators. The variety and number of these instruments which have been developed around the world are legion. This particular technic is still in its early phases and its risk is greater, in our opinion, than that of hypothermia, but it does have the tremendous advantage of giving a much longer period of time to operate within the heart.

We are currently using a modified Gibbon type of apparatus. We are moderately satisfied with this instrument but are sure it can be improved greatly. It has a fixed screen oxygenation system, dual DeBakey pumps, and is capable of delivering about 4000 cc. of oxygenated blood, which is just adequate for a large adult if everything goes well. Our experience with this machine, of course, is much more limited than our experience with hypothermia, but we feel its use is warranted and we will continue to use it for the more complicated anomalies and lesions, such as interventricular septal defect.

Whether hypothermia is used or whether a pump oxygenator is used, it is very important to be able to achieve an adequate approach to all parts of the heart. A large incision is essential. The transverse bilateral anterior scar is the stigma of the patient who has had open cardiac surgery.

Pulmonary Stenosis

DR. S. GILBERT BLOUNT, JR.: The history is of little diagnostic help in valvular pulmonary stenosis. Patients with stenotic lesions of the semilunar valves have few symptoms until the heart fails. One cannot generally depend on symptomatology to reflect the severity of the defect. On the contrary, one should not be lulled into a false sense of security because a patient does not have symptoms. Valvular pulmonary stenosis is a malignant disease, and a patient who is symptom-free may have extreme pressures to 150 or 200 mm. Hg in the right ventricle.

Physical examination is one of the important facets leading to exact diagnosis. It is interesting and quite natural that when one first learns about an anomaly it is the typical case that first comes to attention; then, as more knowledge is gained, the spectrum of the entity becomes more apparent. The classic case

TABLE 3

PROGRESSIVE MORTALITY IN ALL PATIENTS UNDERGOING OPEN HEART PROCEDURES DURING HYPOTHERMIA (192 CASES)

	DEATHS	MORTALITY RATE (PER CENT)
First 48 cases	8	16
Second 48 cases	6	12
Third 48 cases	6	12
Fourth 48 cases	1	2

of pulmonary stenosis is that of the patient who is acyanotic, who has a violent thrill in the second or first left intercostal space, and a harsh, rasping, obstructive type of murmur over this area. The second sound usually is decreased or absent.

We now know that there are great variations in the manifestations of pulmonary stenosis. A patient with severe stenosis may at times have no murmur, or one with minor stenosis may have a considerable murmur. The second sound over the pulmonary area, which is so important, varies greatly; there are two components, as you know, the first being the aortic closure and the second the pulmonary. As the degree of stenosis increases, and as the time of ventricular systole therefore increases, the interval between the two components of the second sound widens. However, as the stenosis becomes more severe, the murmur lengthens so that the first component, the aortic sound, may be obscured entirely by the murmur and one hears only the second component. In the presence of very mild stenosis one hears both components and there can be very definite splitting of the sound, whereas in severe stenosis the murmur goes all the way through the first component and the second or pulmonary component becomes less and less until finally the second sound may not be audible. The murmur, again, varies considerably but is maximum in the second left interspace, though not infrequently in the first one, and always louder in the first than in the third. This is of great importance in differentiating a small ventricular septal defect, the so-called Roger's type.

The electrocardiogram also is important. In the presence of marked pulmonary stenosis it shows the most severe degrees of right ventricular hypertrophy that I know of. There is only one exception, and that is idiopathic pulmonary hypertension. These are the two entities in which pressure within the right ventricle may greatly exceed that within the left ventricle. Thus the presence of definite right ventricular hypertrophy suggests valvular pulmonary stenosis rather than a small ventricular septal defect. The degree of right ventricular hypertrophy in the electrocardiographic tracing in general reflects the severity of the obstruction.

Fluoroscopy is of great value in diagnosis of congenital heart disease. When valvular pulmonary stenosis is associated with a defect in the atrial septum, the lung fields may be clear. Appreciation of the finding of normal vascularity of the lung fields came slowly, because knowledge of pulmonary stenosis stemmed from the tetralogy, where we learned that the pulmonary vasculature almost always was decreased. This is not so in the patient with intact septa. In the tetralogy, all the blood that enters the right ventricle does not go into the pulmonary circulation; a varying amount goes out into the aorta. In valvular pulmonary stenosis with intact septa, all the blood that enters the right side of the heart must go through the pulmonary vascular bed. The heart size may be normal in all respects, and yet there will be considerable hypertrophy of the right ventricle. Poststenotic dilatation is almost always present but is not well correlated with the degree of stenosis. Some of the milder degrees of stenosis will have the greatest poststenotic dilatation, while at times in infancy there is but slight dilatation and it may be difficult to discern.

In more severe stenosis, as the right ventricle begins to dilate it tends to obscure the poststenotic dilatation. One of our patients, a two year old child with severe valvular pulmonary stenosis, was brought to the hospital in failure, with no murmur. Correct diagnosis, of course, was of utmost importance. Yet in the presence of failure in a patient with marked pulmonary stenosis many of the hallmarks of diagnosis are lost. The child was cyanotic, did have a trilogy, and there were clear lung fields and a huge heart.

Diagnosis of valvular pulmonary stenosis, then, is based mainly on auscultatory findings, with fluoroscopy and electrocardiography as ancillary measures.

Which patients do we consider candidates for operation? Of course, one's ideas in this regard change considerably with increasing experience and as confidence is gained in the operative procedure. At present we cannot say that if the pressure in the right ventricle is

100 we operate and that if it is 99 we do not; but usually the pressure is 90 or 100 before we consider operation, although the degree of hypertrophy and enlargement of the heart and other factors influence the final decision. At present we think operation definitely is indicated for any patient with valvular pulmonary stenosis who has a right ventricular systolic pressure above 90 mm. Hg.

DR. SWAN: You will recall that Dr. Brock of London first operated on pulmonary stenosis by the transventricular route. This is a blind method of manipulation of the valve in which one pushes instruments up through the ventricle, and it involves ventriculotomy as well. We were interested in evolving a more direct method of actually seeing the valve and being able to operate on it by a deliberate plastic procedure. The operation which has been developed can be done slowly and deliberately in about three and a half or four minutes of intracardiac operating time, and for this reason it is ideally suited for the rather simple technic of hypothermia.

Through an opening in the pulmonary artery, one looks down on the valve. The operation consists of three incisions into the valve in the lines of the rudimentary commissures, extending from the lumen of the valve all the way to the ring so that the ultimate opening is equal to the size of the ring of the valve. In infants, particularly, we have seen a conical, funnel-shaped valve. Often it is amazing how very small the opening is; it seems incompatible with life, and yet these children in some instances get along fairly well. One sees the very rudimentary little commissures down in the sulcus that never got formed.

In older patients one more commonly sees the commissures extending all the way up to the lip of the valve, and the edges of the valve at the lumen often are quite thickened and fibrosed.

Although one attempts to cut exactly in the commissures, we do not hesitate to cut across the side or adjacent to one of the commissures if necessary. Pulmonary regurgitation, if it occurs to some extent following the procedure, is not a complication of the operation, since it is tolerated extremely well. Further, the diastolic pressure of the pulmonary artery is of such a low order of magnitude that the difference between having a diastolic pressure of, let us say, 12 and having one of 8 does not appear important.

DR. BLOUNT: The results of the operation are interesting. I think the point has been reached in many of these procedures where the surgeon no longer should be satisfied when the patient leaves the operating room alive. We are interested in whether or not we have helped the patient and whether or not the natural history of the disease has been altered. Therefore we have been particularly interested in postoperative evaluation.

Preoperatively, in valvular pulmonary stenosis, pressure tracings reveal low pulmonary artery pressure and very high pressure within the right ventricle. The gradient across the pulmonary valve is some indication of the degree of stenosis. Several months after operation, if the gradient is absent, with systolic pressure within the pulmonary artery equal to that within the right ventricle, for all practical purposes, there is no doubt that the operation has been highly successful. Good pulse pressure also indicates that the stroke volume of the right ventricle is normal.

Isolated infundibular stenosis is a rare anomaly. Almost without exception, infundibular stenosis is associated with a defect in the ventricular septum, but occasionally the latter is intact. We believe we have four such cases. In one, the valve was quite normal, perhaps roughened slightly, with a chamber below it and then a very narrow opening from the body of the main right ventricle into the infundibular chamber. In another, the systolic pressure in the right ventricle prior to operation was 135 mm. Hg. A drop in the diastolic pressure in the infundibular chamber without much change in systolic pressure as compared with that in the pulmonary artery suggested the presence of a third ventricle or intermediate chamber. Postoperatively the systolic pressure in the pulmonary artery was elevated a little (and we have noticed this on occasion), but the gradient, i.e., the stenosis, was completely removed.

Table 4 gives the results of operations to

TABLE 4

RESULTS OF DIRECT-VISION REPAIR OF PULMONARY STENOSIS DURING HYPOTHERMIA (INTACT SEPTA)

TYPE	PATIENTS	CURED	IMPROVED	DEATHS
Valvular	35	33	2	0
Infundibular	4	4		0

repair pulmonary stenosis. There have been 35 patients with isolated valvular pulmonary stenosis and intact auricular and ventricular septa. There were no operative deaths. Nor were there any deaths in the group of four patients with isolated infundibular stenosis. Thus a total of 39 patients with pulmonary obstruction, without any defects in the septa, were cured or improved, without mortality.

Atrial Septal Defect

Atrial septal defect is a fascinating anomaly about which much has been known for many years as far as pathology is concerned. In fact there still is little that can be said to improve the pathologic description given by Rokitansky. However, the clinical diagnosis has been made only in the past 10 or 15 years. It is an easy diagnosis to make in a patient more than two years of age. Any physician whose patients include infants certainly will agree that congenital heart disease in the first months of life is an entirely different problem than it is in older persons.

Again, the history is of little significance in diagnosis; it is the history of any lesion that gives rise to a left-to-right shunt. These children often develop poorly and slowly, gain poorly, and have many upper and lower respiratory infections. They take formula poorly, and often the parents despair of raising them during the first year or two of life. After that, the children seem to adapt to the abnormal hemodynamic situation and begin to improve. There is nothing different in this story from that of the patient with a ventricular defect, anomalous pulmonary venous connections, or patent ductus arteriosus.

Physical examination is again of the greatest importance. These children may be small, and Dr. Taussig has coined the term "gracile habitus." But they are not always small. They are, of course, acyanotic. There is nothing unusual about the deep neck veins. The precordium is hyperdynamic and there are findings of cardiac enlargement. This differs from the patient with valvular pulmonary stenosis in whom there is a systolic overload of the ventricle with a quiet heart, a heart ejecting a normal or actually decreased volume of blood against an obstruction. In atrial septal defect there is a great increase in the stroke volume of the right ventricle, a diastolic overload. There may be a bulging of the precordium. Rarely a thrill is palpable, but frequently palpation reveals a lift to the left of the lower sternum that is suggestive of right ventricular hypertrophy.

Auscultation reveals a murmur that often is slight and not impressive. Rarely one hears a harsh, obstructive type of murmur. It is a murmur that may be considered insignificant and often is passed off as a functional one. Rarely is it more than grade 2 or 2.5 on a 6 basis. It is best heard in the second left intercostal space, well transmitted toward the left shoulder and slightly rough in quality.

The second sound is of great importance, not because of its increase in intensity, for the average patient with atrial septal defect has a normal pulmonary artery pressure, but because of the presence of splitting. The splitting of the second sound is characterized by its width and by the fact that it is fixed. Many normal children have splitting of the second sound that increases on deep inspiration, but the patient with atrial septal defect tends to have a fixed split, that is, the splitting does not increase with inspiration.

Frequently there is a mid-diastolic murmur over the tricuspid area. This murmur formerly was believed to emanate from the mitral valve and to indicate the presence of mitral stenosis. When the combination of atrial septal defect and diastolic murmur was present the patient was said to have Lutembacher's syndrome. We have operated on 91 patients with atrial septal defect and have yet to find one with stenosis of the mitral valve, and the valve has been palpated in each case. This is a func-

tional murmur due to increased flow across the tricuspid valve, not the mitral. However, the term "Lutembacher's syndrome" will stick with us. We are very fond of eponymic designations and are not likely to part with it readily.

The electrocardiogram reveals right ventricular hypertrophy. It is not of a severe degree, and is the rSR′ type.

Fluoroscopically one sees the classic configuration. The first thing one looks for is increased vascularity of the lung fields. The markings are increased, the size of the heart is increased—all right-sided, the right atrium, pulmonary arterial tree and right ventricle.

The right ventricular hypertrophy observed electrocardiographically is the classic type, rarely the severe type seen in valvular pulmonary stenosis. There is discussion as to whether this is a partial right bundle-branch block or selective hypertrophy of the outflow tract.

Thus the diagnosis of atrial septal defect in childhood usually is a straightforward process that may be based on careful clinical evaluation. Typically the child is rather small and has had frequent respiratory infections. Physical findings include a hyperdynamic impulse, the murmur (not prominent), wide splitting of the second sound, and, in about 50 per cent, the early diastolic murmur of functional tricuspid stenosis. The electrocardiogram is quite characteristic, and the rather classic picture is seen fluoroscopically.

DR. SWAN: We are confining this portion of the discussion entirely to the defect of the atrial septum in the upper portion of the septum and are not including the much more complicated lesions which involve the atrioventricular valves or the ventricular septum as well, or the so-called A-V communis.

The operative procedure we employ is an open approach to the right auricle, with suture of the hole in the septum. We recommend the open approach strongly because the variety of the associated malformations of the return of pulmonary venous drainage and, occasionally, the implantation of the inferior vena cava into the left auricle require a rather complex maneuver within the heart so that at the conclusion all the venous blood from the lungs goes into the left auricle and all the vena cava blood, of course, comes into the right. I, for one, am not clever enough to do this without being able to see what I am doing.

The technic of suturing the defect has the satisfying aspect, at least to the surgeon, of making him quite confident that he has in fact tightly closed it and there are no other associated defects.

The final maneuver is getting out of the heart. We formerly used Ringer's solution to avoid trapping air in the auricle, but now we merely release the clamp on one of the venae cavae and let blood fill the right auricle. This has a much better effect on the first few beats of the heart. Instead of Ringer's solution being flushed through the coronaries, good red blood goes through.

The only other important aspect of the procedure, we believe, is postoperative anticoagulant therapy for adult patients with very great enlargement of the pulmonary vascular bed. I am not sure one could appreciate the size of, let us say, a pulmonary artery an inch from the chest wall in an adult who has atrial septal defect unless one had seen it. It is the size of your little finger. Circulation through this tremendous vascular bed is rapidly and drastically reduced by closure of the shunt. Before operation the blood flow through such a pulmonary bed might be 12 l. per minute and immediately following operation it might be 3.5 or 4 l. Such a dramatic change in rate of flow is conducive to intravascular thrombosis in the lungs, and therefore we use anticoagulant therapy as part of adjuvant treatment.

DR. BLOUNT: The patients with atrial septal defect in our series now number 91. For a period of time we recatheterized many of these patients following operation, and at present we have recatheterized 50 of them. The defect has been completely closed in all but three, as evidenced by complete obliteration of the left-to-right shunt. Early in our series we had two patients in whom closure was not complete. At that time Dr. Swan was employing a mattress-type interrupted suture. Since he has used the continuous suture, the defect has been completely closed in every instance.

TABLE 5

RESULTS OF DIRECT-VISION REPAIR OF ATRIAL SEPTAL DEFECT (SECUNDUM) DURING HYPOTHERMIA

	CURE	DEATH	MORTALITY RATE (PER CENT)
First 43 cases	36	7	16
Last 46 cases	46	0	0

The changes are rather dramatic at times. Chest roentgenograms made postoperatively show that the heart is greatly reduced in size with a great decrease in vascularity of the lung fields. One of our first cases was that of a 26 year old woman whose heart was of a classic configuration and huge. Chest roentgenograms made at various intervals postoperatively show that the heart is slightly smaller but still enlarged. We feel this is important, and it is why we believe that every child with this defect should undergo operative repair. If the defect is closed before the period of rapid growth during adolescence, we believe the heart will be relatively normal in size when adulthood is reached. After full growth has been reached, it is doubtful whether the heart ever will return to normal size.

The data in table 5 represent the first 89 patients operated on under direct vision to repair atrial septal defect. Seven of the first 43 patients died. (Certainly some of these were not the best cases that we have presented to Dr. Swan.) The next 46 patients all were cured. Two additional patients have undergone operation since the table was prepared, and there has not been a death among these 48 patients.

We believe that we have reached the point now, at least in our experience, where the indication for operation in atrial septal defect is the diagnosis, just as it is in patent ductus arteriosus.

Trilogy of Fallot

A combination of valvular pulmonary stenosis and atrial septal defect has been termed the trilogy of Fallot. Morgagni first described this combination in 1761—a remarkable description at that time in a 20 year old cyanotic patient. Patients who have this entity may be markedly cyanotic, and all degrees of severity of stenosis and size of the defect are found. Therefore, depending on the two lesions, all types of clinical picture are possible. Occasionally in very mild valvular pulmonary stenosis there is a left-to-right shunt through the septal defect, but usually this is a foramen ovale that has remained open. One out of every four persons, anatomists say, has a foramen ovale that has not sealed, and therefore any condition that markedly increases the pressure in the right atrium and dilates it will open the foramen and give rise at least to a potential area for a right-to-left shunt.

Early in our experience we thought that if we removed the stenosis the defect in the atrial septum might close as the heart size was reduced. We think this may happen occasionally, but certainly not frequently. Several of our patients who were operated on as long ago as five years have almost complete removal of the valvular pulmonary stenosis (complete in some instances) and still are cyanotic due to a right-to-left shunt.

DR. SWAN: The effect of closing the right-to-left shunt in these cases is most dramatic. The reason the patients are cyanotic is because blood is shunting from the right side to the left. After one closes the hole in the atrial septum they immediately become pink.

The technic is exactly as we have already described it. We always do the valve first and then the atrial septum.

Table 6 represents our experience with this condition. It is interesting that it is fairly common. We have seen 17 patients (not too many), and we have done the definitive operation of both procedures in seven. Some of the others were patients whom Dr. Blount described from our earlier experience, and we

TABLE 6

RESULTS OF DIRECT-VISION SURGICAL PROCEDURES DURING HYPOTHERMIA IN PATIENTS WITH TRILOGY OF FALLOT

PATIENTS	OPERATIONS	TOTAL CURE	IMPROVEMENT	DEATH
17	19	7	7	3

may have to reoperate to complete the atrial closure in two or three.

Aortic Stenosis

DR. BLOUNT: Congenital aortic stenosis is rather common. In the past five years it has been somewhat of a surprise to us to realize exactly how common. Certainly it is not the most common congenital lesion, but it makes up about 4 per cent of the cases in our clinic.

Differential diagnosis of obstruction at the aortic valve level and so-called subaortic obstruction or subaortic stenosis is very difficult, and we will not go into this subject here. Clinical impressions often change. Some 10, 15 or 20 years ago subaortic stenosis was considered the more common, and I am sure many of the papers written at that time actually were describing aortic valve stenosis. We now realize, from our operative approach, where one can see and view the valve, that the obstruction is at the valve level in the majority of cases.

Again, this is an obstructive lesion. Usually the child has few symptoms. However, we are most interested in symptoms if episodes of dizziness or syncope occur. We know that sudden death is rather common in aortic stenosis. It may be the first manifestation of disease, or syncopal attacks or dizziness may antedate it. Other than these episodes, the history is of no value, and, of course, once a child has syncopal attacks they are evidence of very severe stenosis.

The child is not cyanotic. The precordium is quiet. Almost always there is a thrill to the right in the first or second interspace, just opposite from that in pulmonary valve stenosis. The heart is not greatly enlarged but there is a sustained thrust down and out where one associates enlargement of the left ventricle. The second sound usually is normal or may be somewhat increased.

It was once thought that one could distinguish between subvalvular and valvular stenosis by the second sound, that if the valve was involved there should be a decreased or an absent second sound over the aortic area and if the obstruction was subaortic there should be a good second sound. This is of very little help, and in valvular stenosis the second sound over the aortic area in most instances is perfectly normal and occasionally is increased in intensity.

The electrocardiogram is very helpful and frequently reveals left ventricular hypertrophy. I believe that evaluation of serial tracings is of great value. Any evidence of rapidly increasing severity in the degree of left ventricular hypertrophy certainly is an indication that one should evaluate the patient carefully and consider operation.

Fluoroscopy is of relatively little value. Vascularity of the lung fields is normal and the heart often is entirely normal in size. The configuration may suggest left ventricular hypertrophy but this is difficult to establish. Often when we examine a child fluoroscopically we say, "Yes, this looks like left ventricular hypertrophy," and I am sure we say it merely because we know that the child has aortic stenosis and there would be no reason for the right ventricle to be hypertrophied.

The diagnosis certainly is based on the finding of the murmur and the changes seen in the electrocardiogram.

I neglected to mention an important point in regard to fluoroscopy. That is the dilatation of the ascending aorta, which is prominent. Normally in a child of five or six years the aorta is inconspicuous. The observation of dilatation in the proximal portion of the ascending aorta is usually helpful in establishing the diagnosis.

DR. SWAN: As one looks down on the cusps in acquired aortic stenosis of rheumatic origin and sees the very great thickening both of the cusps themselves and of the margin and the fusion of the commissure, one realizes the terrific problem in terms of doing anything surgically to allow more blood through the opening. The valve, to palpation, may be almost as hard as a rock, and may consist largely of calcium. Thus the nature of the pathologic process renders this lesion particularly difficult from the surgeon's point of view, and I think most of us are thinking along the lines that it will not really be successfully treated until we have an adequate prosthetic valve to replace it.

We do have an approach to the problem, and one must remember that operating on an

aortic valve is entirely a different problem from operating on a pulmonary valve. The creation of regurgitation of the aortic valve is a disastrous postoperative complication, and, in fact, if one creates, by the operative maneuver, regurgitation of this valve, it may make the patient worse. For that reason, a very precise procedure is necessary.

The approach to the aortic valve also is intrinsically more difficult. It is surprising how far down in the center of the heart this valve lies. There is about an inch of aorta beyond what one can see when one first looks at the heart. Obviously, the dissection is time-consuming and must be done meticulously to avoid injury to the coronary artery. After that, the exposure is essentially the same as it is for pulmonary artery procedures.

It is interesting that if one exposes the ostia of the coronary arteries to the room air there is no tendency whatever for air to enter them. The bugaboo that opening the aorta at this level always results in coronary air embolism is completely unfounded. Air embolism will not occur if one takes great care in getting all the air out of the heart and the aorta at the conclusion of the open portion of the procedure. We take several steps in order to accomplish this.

Experience is, of course, of tremendous importance to the results that one can achieve, and our experience is not yet at all extensive with this operation. We have had 19 patients (table 7), four with acquired disease and 15 with some form of congenital disease. In both forms of the disease, we feel that even though the operation is difficult because of the friable aorta and the pressures put on it and the difficulties in closure and in exposure, if the valve contains some significant portion which is loose and free and will flap, then one can help the patient.

TABLE 7

RESULTS OF DIRECT-VISION REPAIR OF AORTIC STENOSIS DURING HYPOTHERMIA

	PATIENTS	IMPROVED	DIED
Congenital			
Valvular	12*	9	2
Subvalvular	3	1	2
Acquired	4	2	0

*One patient had associated pulmonary stenosis.

DR. BLOUNT: As Dr. Swan already mentioned, we feel that operation definitely is indicated for the infant or child with severe congenital aortic stenosis. Technically the operation is much more difficult than the pulmonary valve operation. In the latter, pulmonary insufficiency is handled very nicely by the heart for years and years, and one does not worry if a minor degree is created. However, it takes exquisite care in the dissection of aortic valve stenosis to dissect down the center of the commissure, because if insufficiency is created it is an entirely different problem.

The problem in the patient with acquired rheumatic aortic stenosis is entirely different. The majority of these patients have calcific aortic stenosis. The valve is markedly deformed and calcified, and with our present approach we feel that only rarely can we help the situation.

Scientific Exhibit

Chemopallidectomy and Chemothalamectomy

for Parkinsonism and Involuntary Movements of Childhood

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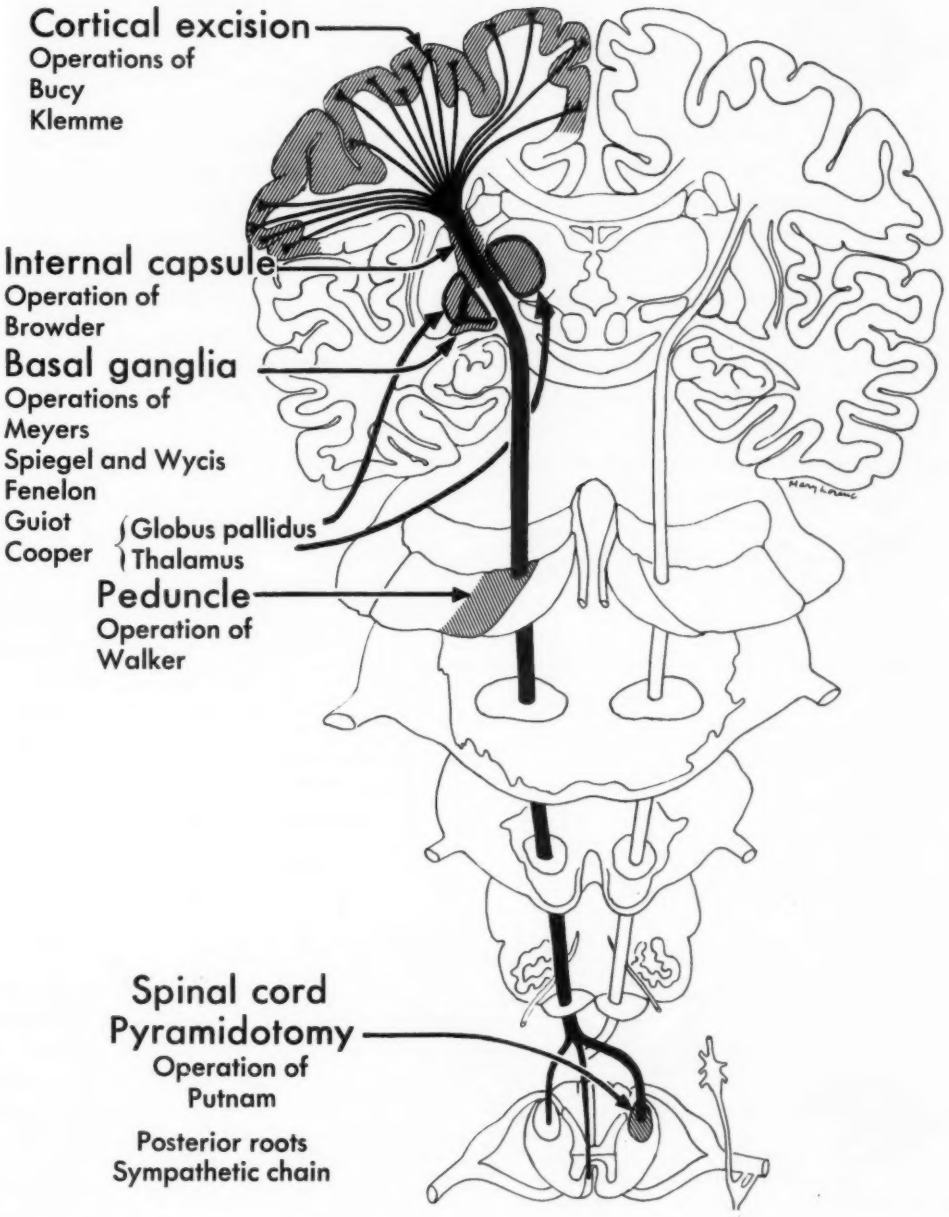
Introduction

VARIOUS neurosurgical procedures have been used in an attempt to relieve tremor, rigidity and other hyperkinetic manifestations of parkinsonism and allied diseases. During the past two decades, destructive procedures have been carried out at every level of the nervous system. Most of these have been directed at the pyramidal tract and have substituted muscular weakness for involuntary movements. More recently it has been demonstrated that certain operations aimed at the basal ganglia are capable of relieving tremor, rigidity and other hyperkinetic manifestations without sacrificing motor power or inducing other neurologic deficit. This exhibit deals with the technic of chemopallidectomy and chemothalamectomy which has been developed by the author.

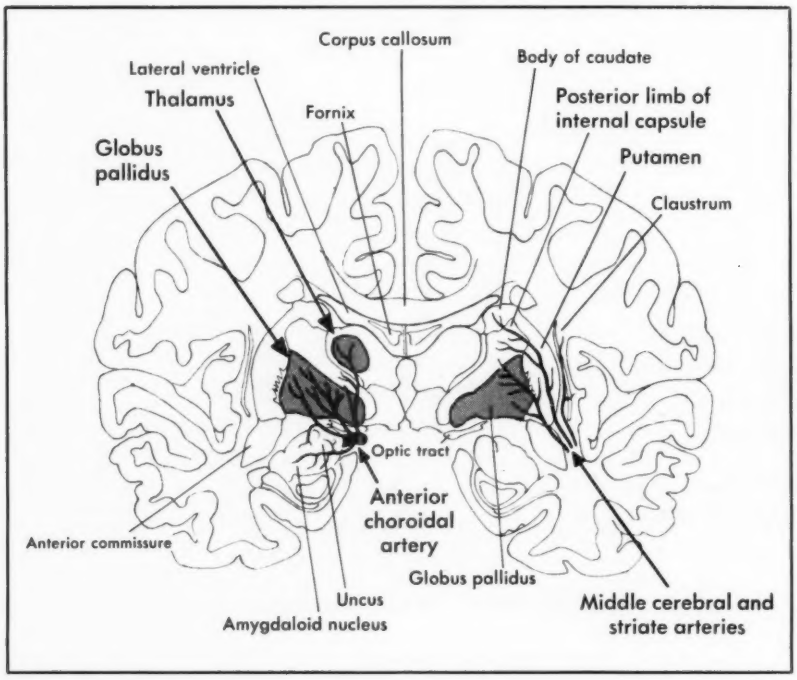


Historical review of neurosurgical procedures for parkinsonism and related disorders.

The Globus Pallidus and Ventrolateral Nucleus of the Thalamus as a "Physiologic Unit" and a Surgical Target

OCCLUSION OF THE ANTERIOR CHOROIDAL ARTERY

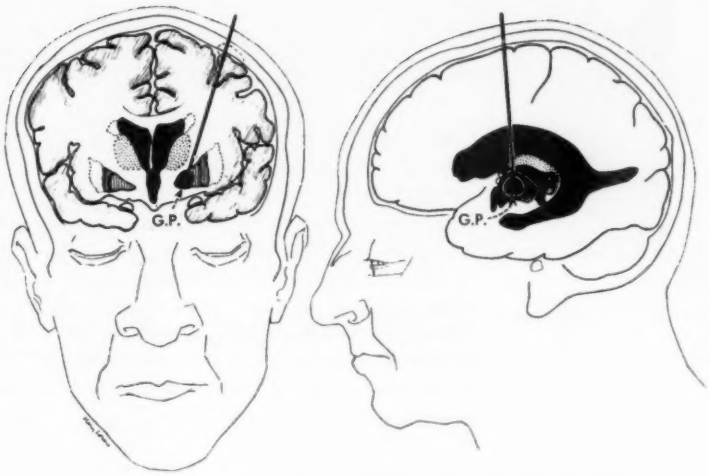
Occlusion of the anterior choroidal artery was first performed in 1952. It was hypothesized that this artery irrigated a physiologic unit consisting of the mesial portion of the globus pallidus, the ventrolateral nucleus of the thalamus, and other extrapyramidal nuclei. Occlusion of this artery in selected cases completely alleviated tremor, rigidity, deformity and incapacitation without inducing any motor weakness. In some of the earlier cases such relief has now persisted for five years, thus demonstrating the possibility of producing five year "cures" of tremor, rigidity and deformity without inducing neurologic deficit. The operation is hazardous in persons more than 60 years of age and involves too great a risk for routine use. However, the data and the results obtained from it led to the development of the subsequent technic, chemopallidectomy and chemothalamectomy.



Occlusion of the anterior choroidal artery.

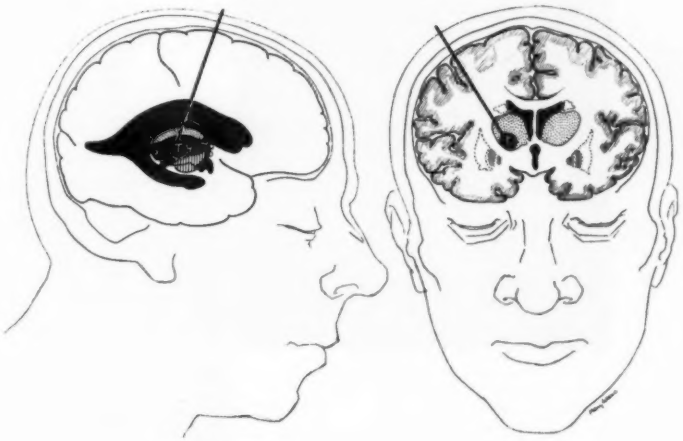
CHEMOPALLIDECTOMY

A polyethylene cannula with a small inflatable rubber balloon at its tip is placed into the mesial portion of the globus pallidus. The balloon is then distended to produce a small cavity in the globus pallidus which will receive subsequent alcohol injections. These injections produce a permanent destructive lesion. Chemopallidectomy is generally used when rigidity is the predominant symptom.



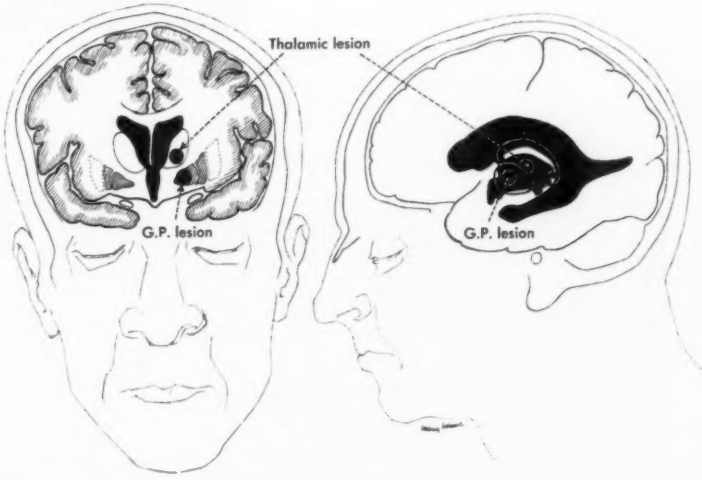
CHEMOTHALAMECTOMY

In chemothalamectomy the cannula is placed into the ventrolateral nucleus of the thalamus. This procedure is generally employed when tremor is the predominant symptom.



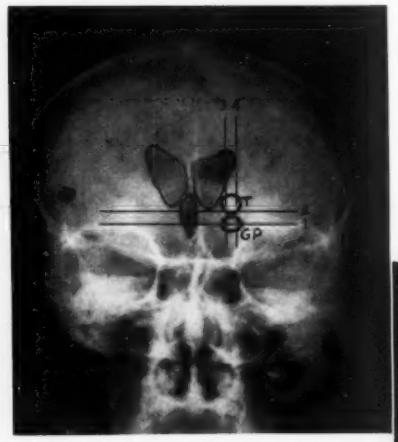
CHEMOPALLIDOTHALAMECTOMY

In some cases it is necessary to create lesions in both the globus pallidus and the thalamus in order to relieve contralateral tremor and rigidity completely. Combined lesions of this type have been produced in approximately 15 per cent of our total series of 700 cases.



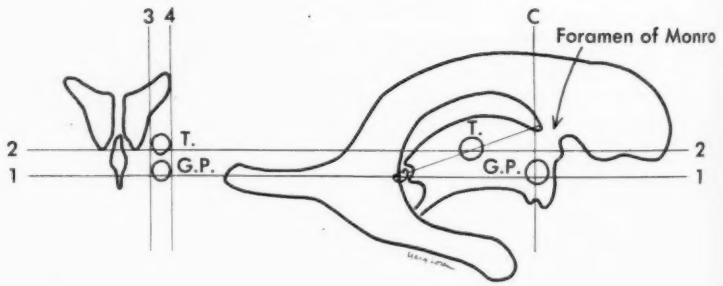
Technic of Chemopallidectomy and Chemothalamectomy

Preoperatively, pneumoencephalography is used to outline the intracerebral ventricles and localize the mesial globus pallidus and ventrolateral nucleus of the thalamus. A tantalum wire is positioned on the scalp to overlie the foramen of Monro, and a corresponding line is scratched on the scalp to represent the plane of the foramen of Monro throughout the operation. A small bur hole is placed 5.5 cm. lateral to the midline on this plane. The chemopallidectomy guide is centered over the line. The cannula holder on the guide overlies the bur hole. The special catheter is inserted a short distance beyond the cerebral cortex, aimed at the proper surgical target.

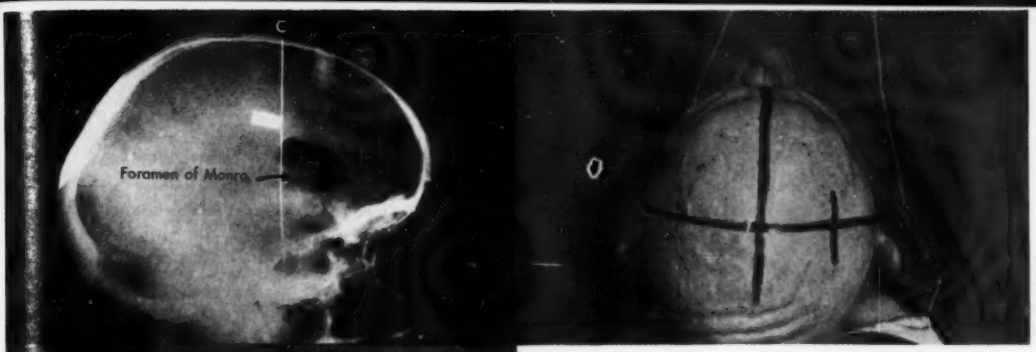


Anteroposterior pneumoencephalogram demonstrating the simple method used to outline the intracerebral ventricles and localize both the mesial globus pallidus and the ventrolateral nucleus of the thalamus.

Lateral projection demonstrating the landmarks for the mesial globus pallidus and ventrolateral nucleus of the thalamus.



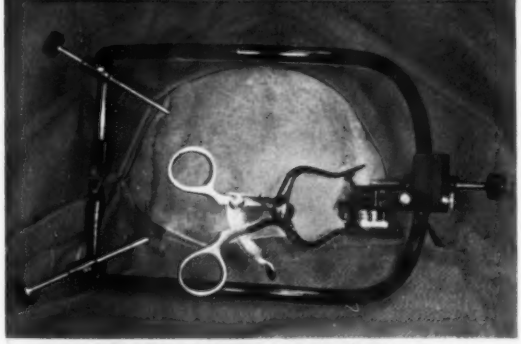
Diagrammatic representation of ventricular landmarks.



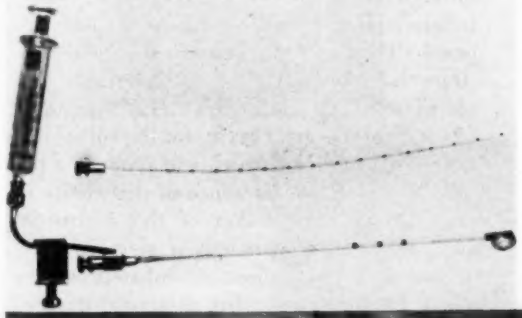
A tantalum wire is positioned on the scalp to overlie the foramen of Monro, and a corresponding line is scratched on the scalp.

Line C represents the plane of the foramen of Monro.

Small bur hole is placed 5.5 cm. lateral to the midline on the plane of the foramen of Monro.



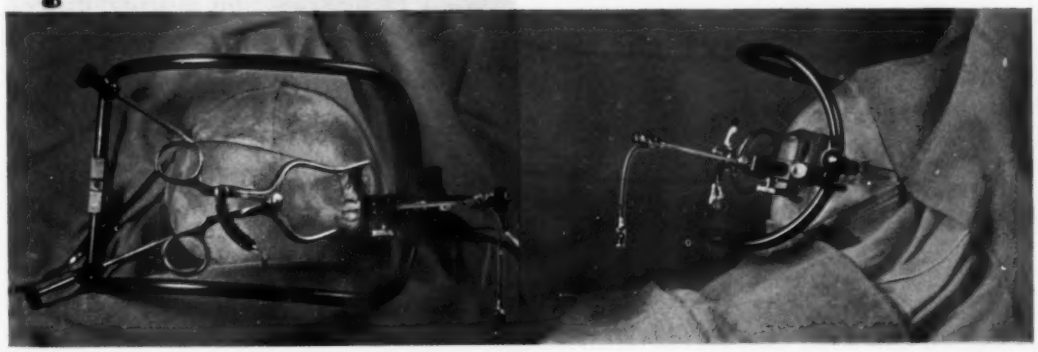
Chemopallidectomy guide is placed on the skull, centered over line C. Cannula holder overlies the bur hole.



Polyethylene cannula with small inflatable rubber balloon at its tip.

Special catheter is inserted a short distance beyond the cerebral cortex, aimed at the proper surgical target.

Side view of catheter inserted.



X-rays are made to be certain the cannula is properly aimed.

X-rays are made to be certain the cannula is aimed properly, and then the cannula is inserted its full depth into the globus pallidus or ventrolateral nucleus of the thalamus. The stainless steel stylet is removed from the cannula and replaced with a soft nylon stylet.

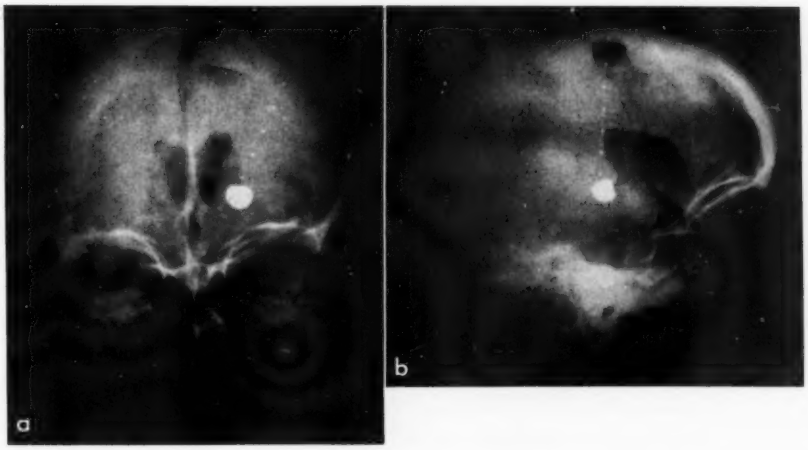
X-ray demonstrating that the cannula is aimed at its proper target, the mesial globus pallidus.

Stainless steel stylet is replaced with soft nylon stylet.

The small balloon at the end of the cannula is inflated with 0.5 cc. HYPAQUE® injected through one of the two lumina of the cannula. Inflation of the balloon serves a dual purpose: (1) It is a physiologic test to demonstrate that a lesion placed in this area is capable of relieving the contralateral symptoms; (2) it creates a small cavity for the subsequent injection of alcohol, which will produce a permanent lesion. The presence of this cavity insures proper localization of the destructive medium. Since the patient is alert and conscious when the balloon is inflated, contralateral tremor and rigidity disappear immediately if it has been properly localized.

Balloon at end of cannula is inflated with 0.5 cc. Hypaque.

In addition to the physiologic check which is made by the condition of the patient at the time the balloon is distended, roentgenographic checks are made prior to completion of the operation.



Proper position of the inflated balloon is checked roentgenographically prior to completion of operation.

The day following surgery, the balloon is deflated; absolute alcohol mixed with PANTOPAQUE® is injected into this prepared cavity in the globus pallidus or thalamus. The patient is conscious, and the size of the injection is determined by his clinical condition and by the roentgenographic appearance of the lesion. Mixture of Pantopaque with absolute alcohol or with a specially prepared viscous alcohol, ETHOPALIN®, causes the lesion to become radiopaque.

The day after operation, the balloon is deflated and absolute alcohol mixed with Pantopaque is injected into the cavity.

Roentgenographic appearance of final lesion produced in globus pallidus by chemopallidectomy.

Roentgenographic appearance of lesion produced in the thalamus by chemothalamectomy.

Results

To the present time, chemopallidectomy or chemothalamectomy or both have been performed in 700 cases on our service. Eighty per cent of the patients have had satisfactory and lasting alleviation of tremor, rigidity, deformity and incapacitation without any neurologic sacrifices. The risk of mortality is 3 per cent. In addition to relieving tremor and rigidity, this procedure has also relieved choreo-athetosis, hemiballism and dystonia.

We recommend surgical intervention for male patients when the signs and symptoms of parkinsonism threaten gainful employment. For women, it should be considered if they are unable to care for their children, perform their household duties, or maintain their jobs, if employed.

Contraindications

1. Organic mental deterioration.
2. Psychosis.
3. Pseudobulbar palsy with inability to swallow or speak.
4. Excessive vegetative symptoms such as hyperpyrexia, hypersalivation, flushing of the skin, and so on.
5. Physiologic old age with marked evidence of arteriosclerosis in a patient who appears much older than he is.
6. Ordinary medical contraindications such as cardiac or renal failure and extreme hypertension.

Advantages of Chemopallidectomy or Chemothalamectomy

1. It produces an accurately localized lesion by a relatively simple technic of cannula placement.
2. It provides a physiologic test by balloon inflation in the globus pallidus or thalamus in the conscious, cooperative patient; one can predict the result prior to inflicting a permanent lesion.
3. The indwelling-cannula technic allows the surgeon to tailor the size of the lesion to the patient's needs. By persistence, one can produce the lesion or lesions necessary to relieve tremor and rigidity.
4. The procedure has been developed, tested, documented and evaluated in a consecutive series of 700 cases over a period of five years.
5. It is capable of relieving tremor, rigidity, incapacitation and deformity completely, and such relief is lasting.

The author wishes to acknowledge the aid of Miss Mary Lorenc, medical artist, and Miss Rosemarie Spitaleri, medical photographer, both of St. Barnabas Hospital.

Parts of these investigations have been assisted by grants from the Sister Kenny Foundation, the Allen P. and Josephine B. Green Foundation, Office of Vocational Rehabilitation, the Albert and Mary Lasker Foundation, and the William Hale Harkness Foundation.

Menstrual Problems in the Adolescent

PENN G. SKILLERN*

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PENN G. SKILLERN

BEFORE the onset of the menses, the anterior lobe of the pituitary body begins to liberate gonadotropic hormone, the ovaries mature, and estrogen production starts. The estrogen production from the ovaries is evidenced by the development of the breasts and the growth of primary sex characteristics including external and internal genitalia. The appearance of axillary and pubic hair is due not to estrogen but to androgenic hormone from the adrenal cortex. Some abdominal distress and vaginal discharge may occur from one to six months before the first menstrual period.

The absence of breast development and menses in a girl who has reached the age of 16 years is regarded as abnormal, and its cause should be sought. With onset of adolescence in many normal girls, however, the ovaries do not function regularly, and several months may intervene between ovulatory periods. Treatment for persistent oligomenorrhea is not indicated in such patients because usually after a year or two the ovaries are functioning normally and the menstrual periods are regular. Treatment is indicated if oligomenorrhea persists after marriage and the patient has difficulty becoming pregnant. Most of the problems associated with uterine bleeding in adolescence may be described as functional; they usually do not require endometrial biopsy, curettage, or other tests to determine their cause, but careful pelvic examination should be done through the rectum.

Amenorrhea Followed by Idiopathic Anovulatory Uterine Bleeding

Amenorrhea followed by a prolonged period of uterine bleeding is due to failure of ovulation and to building up of the proliferative endometrium by estrogen without any progesterone. The endometrium in a patient having that condition usually shows a thick Swiss-cheeselike proliferative hyperplasia. Although a normoplastic proliferative endometrium sometimes is seen, the low hypoplastic type of proliferative endometrium seldom is present.

In the majority of adolescent patients having anovulatory uterine bleeding, estrogen or progesterone need not be administered. However, it is important for the physician to explain the condition to the patient and her parents and to reassure them. In a few patients bleeding is severe and treatment is required. The administration of progesterone usually will stop the bleeding; but, in the patient without hyperplastic proliferative endometrium, combination cyclic estrogen-progesterone therapy may be necessary. Progesterone may be given intramuscularly (50 mg. daily for three days) or orally (10 mg. daily for 10 days). Vaginal suppositorics of progesterone are not satisfactory when there is vaginal bleeding, but they may be used for cyclic ther-

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Adapted from a presentation at the course in Advances in Obstetric Care and Gynecologic Bleeding given at The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute.

apy in doses of 50 mg. every day for five days at bedtime. After the bleeding has stopped for a few days as a result of the administration of progesterone, the patient usually will menstruate heavily for a few days. If progesterone is necessary, it may be administered monthly for three months in the doses previously stated. If it is administered intramuscularly, administration should be started 21 days after the onset of the menses or after starting estrogen; if it is administered orally, administration should be started 15 days after the onset of the menses. If estrogen is necessary, a 1.25 to 1.5 mg. tablet of estrone sulfate may be administered daily for 25 days and stopped for five days. The administration should be repeated for three months.

Causes of Premature Adolescence

Menstrual bleeding in a girl less than 10 years of age is considered premature. However, some normal girls start menstruating at the age of eight or nine years because of spontaneous premature pituitary secretion activated by the hypothalamus. Occasionally, there is spontaneous onset of menstrual bleeding at the age of three, four or five years, with normal menstrual periods and normal ovulatory cycles initiated by the pituitary body. The youngest such patient whom I observed was just three years of age. Any such child must be handled expertly from the psychologic viewpoint; the parents especially must be reassured that by the age of 12 years she will be no different from any other girl. The presence of adult concentrations of follicle-stimulating hormone and a mature endometrium substantiates the diagnosis of premature adolescence initiated by normal spontaneous activation of the pituitary.

Albright's syndrome—The same type of normal spontaneous activation of the pituitary, occurring probably through central nervous system and hereditary influences, is present in Albright's syndrome. This extremely rare condition occurs only in the female, and is characterized by areas of skin pigmentation and multiple fractures of small bones, which are revealed by roentgenologic study.

Tumors—A tumor of the brain may activate the pituitary through the hypothalamus and thereby cause premature adolescence. Hormones from the hypothalamus usually cause the pituitary to function. This is true whether the secretion of hormones begins abnormally early due to a hereditary factor, to tumor, or to unknown premature activities. In patients with central nervous system disease, premature adolescence may be associated with mental retardation as well as neurologic conditions which are not difficult to distinguish.

It is always necessary to check for a granulosa tumor in a girl having premature adolescence. If a granulosa tumor is present, there is uterine bleeding without ovulation. It is much easier to determine the presence of this type of tumor in a child than in a menstruating adult. The presence of pubertas praecox with premature breast growth but no menses may signify the presence of an adrenal tumor. In a case of this type of tumor, the presence of an elevation of the urinary concentration of 17-ketosteroids may be of diagnostic value.

Normal Variations of Ovulatory Uterine Bleeding

There are several normal variations of ovulatory uterine bleeding that may occur at any age. It is especially important, however, that these variations be explained to young patients because they are more likely to be unfamiliar with them and alarmed by them than are older patients.

"Midmonth" staining, which is believed to be due to a temporary estrogen deficiency and to be related to ovulation, sometimes will continue until the beginning of the next menstrual period. However, it is not considered abnormal or alarming in the adolescent. Simple explanation and reassurance will be more beneficial than any other treatment. Explanation and reassurance usually also are the most effective treatment for the patient who is disturbed because she starts to menstruate a few days prior to her regular period. The physician may find that the patient who complains of profuse and prolonged bleeding but does not have anemia is ovulating normally and that her periods are not necessarily abnormal. Again, the patient's condition should be ex-

plained to her as a normal variation, and she should be told that she may bleed in this way for as long as she menstruates. Although a menstrual period longer than seven days usually is considered abnormal, some normal patients menstruate for 10 days regularly in every period.

Another normal variation is represented by the young patient who menstruates more frequently than she believes she should. A patient may believe that she has abnormal menses because a variable time from 20 to 30 days intervenes between the onset of menstrual periods. As long as a patient does not miss a period, I believe that she does not necessarily have an abnormally irregular cycle.

Systemic Diseases Causing Functional Uterine Bleeding

In the case of a young patient who has functional uterine bleeding, one should keep in mind the possibility of the presence of a hematologic disease such as thrombopenia or leukemia. Another disease that may cause functional uterine bleeding, and that is not often considered, is cirrhosis. The bleeding associated with this disease is due to impairment of the liver function so that estrogen cannot be inactivated.

Hypothyroidism should be considered as a possible cause of functional uterine bleeding not only in the adolescent but also in the adult; however, this disease is rare in the adolescent. The importance of hypothyroidism as a cause of menstrual disorders has been overemphasized. Patients who have true primary hypothyroidism causing a disturbance of menstrual function are more likely to have menorrhagia than amenorrhea. Interestingly, many of the premenopausal patients whom I have observed who have true hypothyroidism do not have menstrual disturbances. Other workers, particularly from university centers, have reported a higher incidence of menstrual disorders in cases of hypothyroidism than that observed here. This difference may be accounted for by the fact that the patients, particularly those having struma lymphomatosa, examined in a clinic such as ours are diagnosed in a much earlier phase of hypothyroidism than are the patients who are observed in a number of hospitals.

Use of Desiccated Thyroid for Menstrual Disorders

For years, many endocrinologists have believed that desiccated thyroid has been used far too indiscriminately in the treatment of menstrual disorders. However, there seems to have been a trend in the last few years by many physicians to limit its use. The advisability of limiting its use has been substantiated by Buxton and Hermann[1] in a study in which they compared two groups of euthyroid patients with sterility or menstrual disorders. Of the initial 339 patients studied, only 131 were considered for final analysis. The 75 patients in group A were treated empirically with thyroid extract. The 56 patients in group B were given only placebo tablets. The thyroid function of each patient was investigated at regular intervals by determinations of basal metabolic rate, protein-bound iodine concentration, radioactive iodine uptake, and serum cholesterol concentration. The difference between the improvement rates of the two groups was not statistically significant. It was the authors' impression that the administration of exogenous thyroid to these euthyroid patients did no more therapeutically than did the administration of the placebo. The administration of desiccated thyroid depressed the patient's own thyroid function. As soon as the administration of desiccated thyroid was discontinued, the patient's thyroid gland resumed normal function.

However, if it is necessary to treat patients having true primary hypothyroidism, I still prefer to give the uncoated U.S.P. desiccated thyroid in daily doses of 2 gr. rather than the newer pharmaceutical preparations, which are two to four times as expensive. While a rare patient with true hypothyroidism may not respond to potent uncoated desiccated thyroid, we have not observed such a patient in our institution.

REFERENCE

1. Buxton, C. L. and Hermann, W. L.: Effect of thyroid therapy on menstrual disorders and sterility. J.A.M.A. 155:1035 (July 17) 1954.

The Acute Surgical Abdomen in the First Year of Life

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Tulane University School of Medicine, New Orleans

MARSHALL L. MICHEL

THE acute abdomen in the first year of life is a serious problem for the surgeon as well as for the pediatrician or general practitioner. It differs in many respects from the acute abdomen in other age groups. The history is frequently indefinite and inadequate. Physical examination of the abdomen is unsatisfactory in an infant with acute abdominal pain. Tenderness, rigidity and masses are difficult to detect and to evaluate. Because of the shortcomings of both the history and physical examination, roentgenologic and laboratory studies must be particularly complete. The physician must keep in mind that extra-abdominal conditions often produce abdominal symptoms in infants.

The pathologic conditions usually encountered in cases of the acute abdomen in the first year of life differ from those found in other age groups. Common causes of the acute abdomen in older age groups such as acute appendicitis, adhesive obstruction, acute gynecologic conditions, colonic diverticulitis and malignant colonic obstructions almost never occur in infancy.

I shall discuss various surgical conditions that produce acute abdominal symptoms in the first year of life. As a basis for analysis, the records of 100 consecutive cases of acute abdomen in the first year of life from Touro Infirmary and Charity Hospital in New Orleans were studied. In all these cases, an obstructive lesion was found. The acute abdominal surgical condition as the result of an inflammatory process is very uncommon in this age group.

Incarcerated Inguinal Hernia

Incarcerated inguinal hernia was present in 30 of the 100 cases. It is the most common acute abdominal surgical condition in the first year of life. Treatment differs from that in other age groups. When the patient is an adult, immediate operation usually is indicated because of the danger of strangulation. In infants, strangulation rarely occurs. One should

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reduce the hernia carefully by manual manipulation after elevating the lower extremities and administering sedatives parenterally (LUMINAL® sodium and codeine). Operation is best postponed for 24 to 48 hours, until the edema surrounding the thin hernial sac has subsided. The operative approach should be through a small transverse incision over the internal inguinal ring. High ligation and excision of the sac are all that is necessary. Because there is no fascial defect in the floor of the inguinal canal, reconstruction of the canal is not required. All inguinal hernias in infants should be repaired promptly by elective operation, since the incidence of incarceration is high. Spontaneous cure of inguinal hernia probably never occurs.

Incarcerated Umbilical Hernia

There were 19 instances of incarcerated umbilical hernia in the 100 cases. Umbilical hernias generally are not treated by means of elective operation during the first year of life because the majority disappear spontaneously. However, incarceration with intestinal obstruction occasionally does occur. As in instances of inguinal hernia, it is best to reduce the hernia manually and operate after one or two days. However, manual reduction frequently is impossible and emergency operation is necessary. A transverse subumbilical incision, slightly curved with the concavity upward, is the incision of choice. In this manner the umbilicus is preserved. Transverse overlapping repair of the fascial defect can then be performed.

Pyloric Stenosis

Pyloric stenosis was the pathologic entity in 24 of the 100 cases. Although strictly speaking it cannot be considered an acute abdominal condition, since the symptoms usually begin gradually and have an onset that usually lasts two or three weeks, it is definitely not a chronic situation. I have included it because of its urgency. The infants are most often males and frequently are first-borns. Vomiting begins two or three weeks after birth and eventually becomes projectile. A tumor mass often is palpable in the right upper abdominal quadrant. LIPIODOL® or HYPAQUE® visualization of the stomach verifies the diagnosis. Operation is urgent but should not be done as an emergency. One should achieve a state of optimal hydration and nutritional replenishment by parenteral methods (infusions, transfusions, vitamins, and so on). The operative procedure of choice is the classic pyloromyotomy (Fredet-Ramstedt operation).

Intussusception

Intussusception was the cause of the acute abdominal condition in 19 of the 100 cases. Intussusception occurring during the first year of life usually is of the primary type, that is, there is no precipitating pathologic condition such as Meckel's diverticulum or intestinal polyp. Primary intussusception most often occurs between the fifth and tenth month of life. The onset is sudden, usually in a healthy, vigorous child. Severe abdominal pain, vomiting and melena are the classic symptoms. Frequently a mass is palpable in the right side of the abdomen or the midabdomen. A barium enema will verify the diagnosis. Most of these obstructions are of the ileocecal variety. Reduction by means of the barium enema sometimes is possible. We do not advocate this procedure for treatment because of the danger of incomplete reduction or perforation. Operative treatment is simple and expedient, and preferred.

Intestinal Atresia

Intestinal atresia accounted for four of the 100 cases. The classic symptom is bile-stained vomitus (green or yellow) on the first or second day of life. A feeble premature infant may not vomit, but the nasal or oral secretions may be green or yellow. A plain roentgenogram of the abdomen will verify the diagnosis, showing distended bowel above the atresia and a totally empty bowel below. A simple side to side intestinal anastomosis around the site of obstruction is curative.

Malrotation

Intestinal malrotation, causing intestinal obstruction, occurred in two of the 100 cases. Disturbances of rotation usually cause one of

two types of obstruction: (1) extrinsic duodenal obstruction and (2) midgut volvulus.

Extrinsic duodenal obstruction—This situation actually is due to incomplete rotation rather than malrotation, although the latter term is most often used. The cecum fails to descend into the lower right abdominal quadrant, remaining in the subhepatic region. Compression by the cecum and by congenital subhepatic peritoneal folds causes obstruction of the descending duodenum. Vomiting of bile-stained material is the primary symptom. Rapid dehydration ensues. Abdominal distention is minimal because of the height of the obstruction. The roentgenographic picture is similar to that of duodenal atresia although the obstruction may not be complete. Operative relief is simple. The subhepatic peritoneal folds are severed and the cecum is completely mobilized into the upper left abdominal quadrant, allowing the entire colon to remain in the left side.

Midgut volvulus—This is the most serious of all intestinal obstructions in the newborn period. It is the result of a short mesenteric attachment allowing hyperrotation of the midgut. Rotation may occur either in the physiologic (counterclockwise) direction or in the opposite direction. Either way, the rotation may reach a degree at which both luminal and vascular obstruction of the midgut occurs. These infants are very ill. Distention and vomiting are severe. Circulatory collapse is frequent. Abdominal roentgenograms may be inconclusive because luminal obstruction may not be complete although strangulation due to mesenteric torsion may be present. Immediate operation is necessary. Detorsion with mobilization of the entire colon into the left side of the abdomen is indicated. If gangrene of the intestine is present, resection with primary anastomosis is the procedure of choice.

Intestinal Duplication

Duplication occurred in one of the 100 cases. Duplication of the intestinal tract may produce acute abdominal symptoms in infancy in three ways: (1) obstruction, (2) hemorrhage and (3) ulceration, with evidence of acute inflammation. The duplication is more common in the ileum than in other locations, and treatment of choice is excision of the involved area and end to end anastomosis to restore continuity. When the duplication occurs in another location such as the stomach, rectum or duodenum this operative procedure is not applicable. The one case of duplication in the series of 100 cases was a duodenal duplication in close proximity to the common bile duct. Resection would have been too formidable. Therefore the cystic cavity of the duplication was anastomosed to a loop of jejunum to permit drainage. A side to side jejunojejunostomy was done below the first anastomosis. The patient has been well since operation.

Postoperative Adhesions

Only one of the 100 cases was due to postoperative adhesions. This is an unusual cause of intestinal obstruction in infancy but is common in adulthood. The adhesive obstruction in the aforementioned case followed the release of an ileocecal intussusception.

This series of 100 cases by no means illustrates all the conditions that produce the acute abdomen in the first year of life. The discussion would be incomplete without considering also Meckel's diverticulum, meconium ileus and acute appendicitis, although these conditions did not account for any of the 100 cases studied.

Meckel's Diverticulum

The most common cause of massive bleeding from the gastrointestinal tract in the first year of life is peptic ulceration in a Meckel's diverticulum. In such diverticula an aberrant area of gastric mucosa produces a peptic type of ulceration either in the diverticulum or in the adjoining ileum. Hemorrhage can be extremely severe. Other complications of Meckel's diverticulum such as obstruction and inflammation are rare in the first year of life.

Appendicitis

A most interesting observation is the almost complete absence of acute appendicitis during the first year of life. When it does occur in this age group it manifests itself usually as a generalized peritonitis. Operative treatment

should be prompt because the condition is very serious in the small infant.

Meconium Ileus

This is an extremely severe form of intestinal obstruction that occurs most often in the first year of life. It is the result of an accumulation of large amounts of inspissated meconium throughout the small intestine. The condition is associated with chronic cystic disease of the pancreas and a marked deficiency in exogenous pancreatic secretions. Treatment of choice is laparotomy with one or more operative enterotomies and manual removal of the meconium. Irrigations through the enterotomy openings with saline, peroxide and other solutions have given successful results. Pancreatic enzymes should be introduced directly into the enterotomy openings at operation. Postoperatively one should administer pancreatic enzymes by mouth as soon as the infant can tolerate oral feedings.

Summary

An analysis of 100 consecutive cases of acute abdominal conditions in the first year of life shows that the problem of the acute abdomen is different during this period than it is at other ages. Also, numerous conditions which are common in later life rarely occur in the first year. It is interesting that in this series one infant survived three acute abdominal procedures (incarcerated hernia, intussusception and adhesive obstruction). A correct understanding of the problem can result in a low mortality rate (2 per cent in the series reviewed). Death occurred in one case of intestinal atresia and one of midgut volvulus.

1958

INTERSTATE POSTGRADUATE MEDICAL ASSEMBLY

Nov. 10-13 Municipal Auditorium Cleveland, Ohio

Juvenile Eczema

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Eczema in young people during the adolescent years may be a mild affliction or it may be generalized and disabling. Often it is associated with a background of hay fever or asthma, as well as eczema in infancy. There is a great deal of discussion and argument as to how much can be accomplished in these cases by allergic investigation, including skin tests, diets and attempts at hyposensitization. In this group, too, psychosomatic features have been emphasized. Persons with juvenile eczema or atopic dermatitis have a peculiar constitution with measurable abnormalities in the skin and the nervous system. Occasionally cataracts appear as an unexplained complication. Outlines of typical case problems will be presented and a practical rule of management discussed.

Physiology of the Thyroid Gland

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LESLIE J. DE GROOT

HISTORY credits Galen with noting the presence of the thyroid gland, and Vesalius with describing its anatomy in 1543. About three centuries later, in 1835, the clinical picture of Parry's or Graves' disease was elucidated.[1] The function of the normal gland was not fully appreciated until Kocher[2] perfected surgical thyroidectomy sufficiently for patients to survive the operation and ultimately to have hypothyroidism. In 1885, Horsley[3] formulated a clear concept of myxedema, distinguishing it from the frequent complicating symptoms caused by recurrent nerve and parathyroid damage. Murray[4] introduced the use of animal thyroid tissue for replacement therapy in 1891.

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As in other areas of scientific investigation, the progress in this field seems to have moved at a rapid rate. In the last two decades, knowledge of thyroid physiology has grown in geometric progression. This growth has been stimulated by the development of accurate methods for determining small amounts of iodide, by the use of radioisotopes of iodine, and because of the broad application of partition chromatography technics. At present, the formation, distribution, metabolism and metabolic action of thyroid hormones are being related to specific enzymatic reactions at the cellular level. It seems probable that solutions to perplexing problems such as nodular goiter and Graves' disease are not distant.

Anatomy

The thyroid gland develops largely from a midline outpouching of the embryonic pharyngeal floor. A pair of lateral elements arising from the fourth pharyngeal pouches may furnish a small portion of glandular tissue.[5] During fetal growth, the embryonic gland

descends from the area of the midline pouch at the base of the tongue in close association with the rudimentary heart and thymus. Faulty development can lead to deposits of tissue in the anterior midline of the neck from tongue to mediastinum. The descending gland remains attached by a hollow stalk to the pharyngeal floor near the base of the tongue, thus forming a thyroglossal duct. If this duct is not totally obliterated during fetal development, cysts may form along its course during adult life. A pyramidal lobe, usually a paramidline strand of tissue jutting upward from the isthmus, is the lowest segment of the thyroglossal duct and is present in a majority of adults.

The adult butterfly-shaped gland, weighing from 20 to 30 gm., straddles the first two cartilaginous rings of the trachea. The paired lateral lobes are connected by an isthmus of variable size. The parathyroid glands are intimately associated with the thyroid's posterior surface, and the recurrent laryngeal nerves pass under the lower poles, which accounts for their vulnerability at operation. The older literature mentions aberrant thyroid tissue in the paratracheal area. It is agreed at present, however, that the lateral aberrant thyroid rest is not an embryologic rest, but rather is a metastasis to a cervical node from an occult primary thyroid tumor.

The gland receives its blood supply from at least four arteries. The paired superior thyroid arteries are branches of the external carotid. The paired inferior thyroid arteries are branches of the thyrocervical trunk.

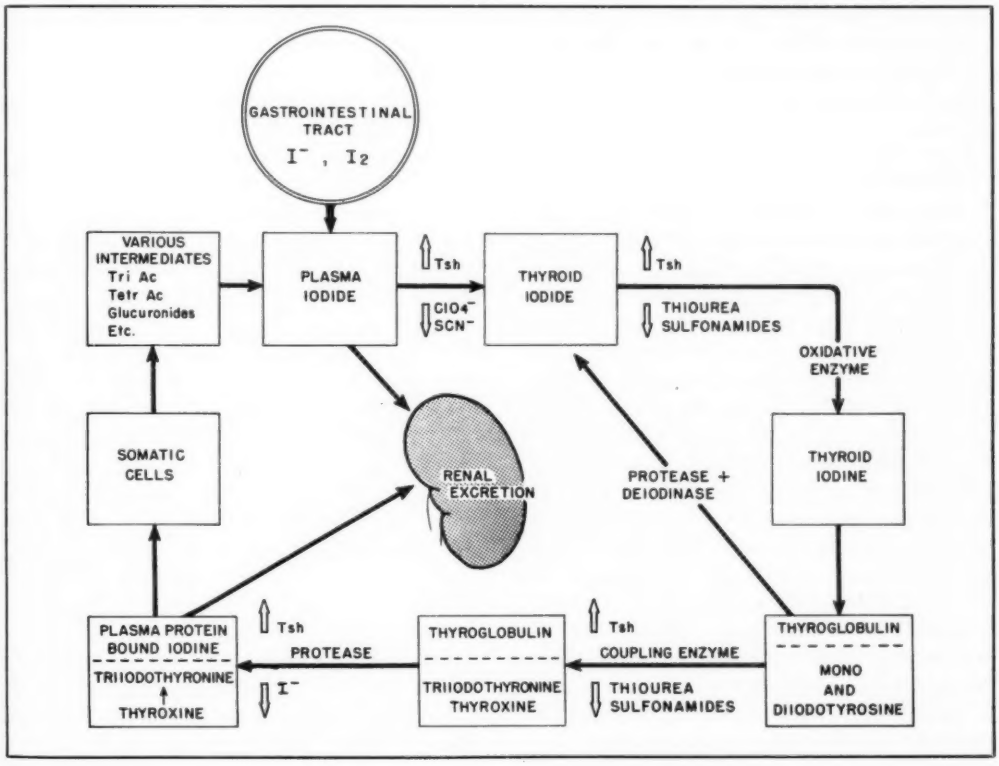


FIGURE 1. The iodine cycle.

(From Stanbury, J. B. and McGirr, E. M.: Sporadic or non-endemic familial cretinism with goiter. Am. J. Med. 22:712, 1957.)

Lymph drainage is to paratracheal, supraclavicular and, less frequently, mediastinal nodes. There is an abundant plexus of autonomic nerves in the gland that presumably are vasomotor fibers. No secretory fibers have been identified.

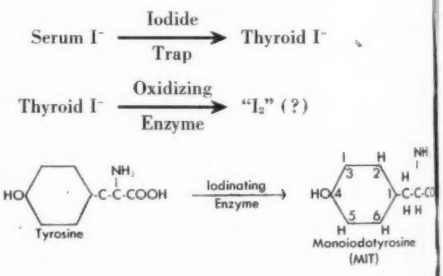
The tissue is divided by fibrous septa into lobules. On closer examination, the latter are found to consist of clusters of discrete, oval or round, completely closed follicles averaging 300 μ in diameter. The cells forming the follicle are normally about 15 μ in height. The center of the follicle is filled with thyroglobulin, a protein colloid. Histochemical technics have demonstrated the usual ribose nucleic acid in the cell protoplasm and desoxyribose nucleic acid in the cell nucleus. The thyroglobulin stains as a glycoprotein.[6] Electron microscopy has revealed that the border of cells abutting the colloid is thrown up in small projections,[7] suggesting that this border is active in secretion and adsorption. Mitochondria, microsomes, droplets and a well-defined Golgi apparatus also have been detected in the cells.

Physiology

Physiology of the thyroid gland is intimately bound to the metabolism of iodine (figure 1). The average diet contains 100 to 200 μg. of iodide per day, which is absorbed largely in the small intestine. The absorbed iodide is transported in plasma loosely attached to proteins in a concentration of roughly 5 μg./1 plasma. It rapidly equilibrates through a diffusion space equaling about 35 per cent of body weight. Although iodide is excreted by the salivary glands, stomach, mammae and part of the small intestine, these routes are of minor importance. Roughly, two-thirds of ingested iodide is excreted by the kidneys, and one-third is removed by the thyroid. These two organs compete in removing iodide from plasma; therefore, their plasma iodide clearances are reciprocally related.

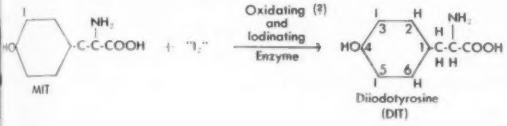
Iodide metabolism within the thyroid consists of the following consecutive steps: (1) clearance of iodide from plasma, (2) oxidation of iodide, (3) attachment of iodine to tyrosine, (4) coupling of iodotyrosines to form iodothyronines, (5) storage of iodothyronines in the colloid, and (6) release of iodothyronines to plasma. The clearance of iodide from plasma and its concentration within the thyroid is an energy-dependent process. Normally rapid oxidation of concentrated (trapped) iodide prevents accumulation of any significant amount of inorganic iodide within the cell. However, the presence of a concentrating mechanism can be demonstrated by administration of a drug such as propylthiouracil that inhibits the oxidative process.[8] It will then be found that the concentration of free iodide in the gland is roughly 25 times that in the serum. (It should be noted that total thyroid iodine would be decreased by administration of this blocking agent.) The ratio of tissue to serum iodide observed in the presence of an oxidation-blocking agent is directly related to thyroid activity. The ratio is depressed by hypophysectomy and increased by TSH (thyroid-stimulating hormone) administration.[9] Certain anions such as KSCN[10] and $KClO_4$ compete with iodide in the trap but are not concentrated themselves. This inhibition of iodide trapping explains the therapeutic usefulness of the latter drug in controlling hyperthyroidism.

Trapped iodide is rapidly oxidized and bound to tyrosine, forming monoiodotyrosine (MIT). In essence the process is:

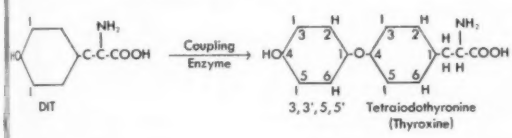


The actual biochemistry of in vivo iodide oxidation and binding is not known. Several known enzyme systems (peroxidase, xanthine oxidase, polyphenol oxidase) have sufficient oxidative potential to oxidize iodide, but as yet the enzyme system active in the thyroid gland has not been identified. It is not known whether the initial oxidation forms I_2, a prod-

uct such as HIO, or a reactive intermediate bearing an oxidized iodine molecule in weak linkage. The oxidation and organification are not necessarily separate steps as diagrammed. Iodine has not been demonstrated in the thyroid, and most investigators believe it is not the iodinating agent active in vivo. In any event, an oxidized atom of iodine is somehow joined to a tyrosine radical in position 3 in the phenyl ring. This is rapidly followed by the addition of another I atom in the 5 position, forming diiodotyrosine (DIT).



The next theoretical step is the coupling of two molecules of DIT to form tetraiodothyronine (thyroxine, T_4).



Presumably, all of these reactions are enzymatically mediated. The finding of protein-bound radioactivity in the colloid within a few seconds after injection of RaI^{131} suggests that the iodination of tyrosine and its coupling occur with tyrosine actually in the amino acid chain of the thyroglobulin molecule.[11]

All of these reactions can be duplicated in the test tube under certain conditions.[12] The formation of MIT occurs quite widely in nature, and several other tissues of the mammalian body are able to form MIT in vitro.[13,14] Perhaps the unique aspect of the thyroid is its ability to concentrate iodide.

Recent work has shown that other iodothyronines are formed within the gland, possibly by random coupling of MIT and DIT.[15] Of the iodothyronines formed, only thyroxine and the 3, 5, 3′ tri-iodo analogue (tri-iodothyronine) are considered to be physiologically important.

As oxidation proceeds in the gland, MIT, DIT, tri-iodothyronine and thyroxine are formed in the thyroglobulin molecule and stored in the colloid. Hormone is made available to the body by a protease in the colloid that breaks down thyroglobulin, liberating the thyroxine and tri-iodothyronine.[16] In the process, MIT and DIT are also liberated, but another cellular enzyme removes the iodine from these compounds, allowing the cell to retain the iodide for reutilization.[17] Only in pathologic states caused by handling of the gland at surgery, by radiation, by carcinoma, and by thyroiditis does thyroglobulin gain access to the serum. In other conditions, including thyroid carcinoma and certain instances of congenital goitrous hypothyroidism, fragments of thyroglobulin seem to be released through some metabolic error[18,19] and may be detected in the serum.

As pointed out by Garrod[20] many years ago, intensive study of the rare patients demonstrating some congenitally determined aberrant metabolic pathway can greatly aid our understanding of normal physiology. Some patients have been found who are able to concentrate iodide effectively but whose glands rapidly lose the trapped iodide back into the serum.[21] These patients have a congenital absence of the enzymes involved in oxidation of iodide or in its organification, and therefore cannot process the iodide through the usual metabolic chain. Another group of goitrous hypothyroid patients excrete MIT and DIT in their urine.[22] These patients lack the intrathyroid enzyme responsible for de-iodinating iodotyrosines. MIT and DIT are not de-iodinated and leave the thyroid gland with the iodothyronines. The MIT and DIT are excreted in the urine, leaving the patient with a chronic lack of iodine. At least one patient has been found with high concentrations of MIT and DIT in the thyroid, but minimal tri-iodothyronine or thyroxine in the serum.[23] This patient presumably lacked the coupling enzyme. Another aberrant metabolic pathway recently has been described in a patient who presented congenital goitrous hypothyroidism and in whose serum peptide-linked iodotyrosines and iodothyronines were detected. Here the defect seemed to be in the abnormal syn-

thesis or degradation of thyroglobulin.[19]

Of recent interest has been the demonstration of antithyroglobulin antibodies in the serum of patients with thyroiditis.[24] These antibodies may be present in amounts large enough to increase the gamma globulin concentration. Many of these cases have nonbutanol-extractable iodine in their serum, which may represent thyroglobulin. It is not yet known whether the auto-antibodies initiate the disease process or are secondary to the liberation of thyroglobulin into the plasma through some primary disease of the thyroid.

The release of thyroxine into the serum is a function of the thyroid gland's level of activity. The release rate is accelerated by exposure to cold environment and pituitary TSH, and decreased by thyroxine administration, probably by pituitary depression.[25] Free thyroxine apparently exists in the thyroid at a concentration greater than that in plasma and is in equilibrium with plasma thyroxine. The equilibrium between free gland thyroxine and free plasma thyroxine ultimately may determine the rate of release of thyroid hormone.

Released thyroxine is transported in the plasma loosely attached to a glycoprotein named the thyroxine-binding protein (TBP).[26] On electrophoretic examination, TBP travels in the interalpha zone of the serum globulins. Although it is tempting to speculate that TBP might represent a fragment of thyroglobulin secreted into the plasma, no present evidence supports this hypothesis. If the normal amount of plasma thyroxine is roughly tripled, it saturates the binding sites on the available TBP, and thyroxine spills over to and is bound by the serum albumin. Tri-iodothyronine binds to TBP less firmly, and even at low plasma concentrations more is found associated with the albumin. The TBP concentration varies directly with the estrogen activity, whether the latter is endogenously or exogenously supplied. The significance of this relationship is not yet obvious.[27] Since the reaction $T_4 + TBP \rightleftarrows TBP.T_4$ is reversible, a small fraction of the plasma thyroxine is free. Speculation exists as to whether this thyroxine may be the quantity controlling the rate of entry of thyroxine into the body cells. On the other hand, thyroxine may enter cells attached to TBP.

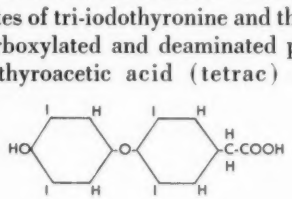
In the euthyroid state 6 ± 2 μg. per cent of hormone is present in the plasma, as measured by protein-bound iodine (PBI). This quantity is elevated in hyperthyroidism and decreased in hypothyroidism. When accurately determined, it provides an excellent (though not infallible) index of thyroid function. A constant portion, roughly 11 per cent, of the thyroxine in the serum is degraded daily. This equals 50 μg. to 150 μg. iodide in the euthyroid state.

Once in the cell, thyroxine stimulates coenzyme A and the activity of several enzymes, including amino acid oxidase, hexokinase, and cytochromoxidase. One dramatic effect of thyroxine is to uncouple oxygen uptake and high-energy phosphate bond formation in mitochondrial preparations.[28] Superficially, the uncoupling action appears to be a metabolically wasteful phenomenon and may not be the important intracellular action of thyroxine.

The net effect of the stimulation of intracellular enzyme systems is familiar to all because of the increase in the basal metabolic rate, activity, basal temperature, pulse, creatinuria, nervous excitability, and nitrogen loss, the decrease in plasma cholesterol, and other phenomena observed clinically after thyroxine administration.

Roughly, four-fifths of the organic iodine released by the thyroid is normally thyroxine, and probably one-fifth is tri-iodothyronine. It is not known whether the ratio of thyroxine: tri-iodothyronine secretion varies in disease states. Of these two established thyroid-secretion products, tri-iodothyronine is almost twice as active per unit weight as thyroxine. Further, its onset of action is more rapid, averaging about two days, in contrast to four to five days for thyroxine.

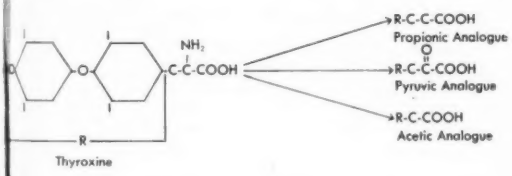
Recent interest has centered about certain metabolites of tri-iodothyronine and thyroxine, the decarboxylated and deaminated products, tetraiodothyroacetic acid (tetrac) and tri-



Tetrac

iodothyroacetic acid (triac). Some evidence suggests these compounds have an onset of action much more rapid than either of the parent molecules,[29] although there is no general agreement on this point. They are about one-fourth as active in the human per unit weight administered. It is possible that these acetic acid analogues comprise the tissue form of the hormone.

The iodothyronines can be metabolized by conjugation, de-iodination, deamination or decarboxylation.[30,31] It is possible that one or more of these steps are necessary to change thyroxine into an active form. Adversely, these processes may only represent pathways for degradation. Mammalian liver contains an enzyme that conjugates thyroxine into a glucuronide[32,33] in the presence of uridin diphosphate glucuronic acid. The product is subsequently excreted in the bile. The glucuronide is broken down in the intestine by bacterial glucuronidases, and most of the thyroxine is resorbed. This cycle is teleologically fascinating, but in man it is physiologically of small importance. In obstructive jaundice, thyroxine-glucuronide may be in the plasma.[34] Using liver, kidney and brain slices, it has been demonstrated that thyroxine and tri-iodothyronine can be deaminated and decarboxylated to form several metabolites.[31] Formation



of these metabolites may be necessary prior to de-iodination. De-iodination of iodothyronines has been reported in several tissues in vitro.[35] It obviously occurs widely in the body, because over 95 per cent of iodine leaving the body is excreted in the urine as inorganic iodide.

The iodide broken off the thyroxine molecule enters the serum and mixes with ingested iodide. Its fate then is to be either excreted by the kidney or again cycled through the pathway just outlined.

Thyroid and the Other Endocrine Glands

The pituitary normally controls the level of the thyroid activity by a feedback mechanism. Present evidence suggests that a reduction or elevation in the plasma PBI level affects a receptor center in the hypothalamus. This in turn regulates the anterior pituitary activity by means of a secretion carried to the pituitary via the hypophysial-portal system of blood vessels.

A *decrease* in PBI ultimately stimulates certain basophilic cells (thyrotrophs) in the anterior pituitary gland to produce increased amounts of TSH (thyrotropin). This hormone is released into the blood; it circulates to the thyroid, and causes increased thyroid iodide trapping, more rapid iodide oxidation and binding, and more rapid thyroglobulin proteolysis, and increases the rate of release of thyroid hormone. When the plasma PBI level is raised once again to the desired level, the hypothalamic receptor center decreases further TSH output. The receptor center has been demonstrated in rats whose anterior hypothalamic nuclei have been injured by electrocoagulation.[36] These animals do not grow goiters in response to administration of an antithyroid drug.

The method by which plasma PBI level is translated into stimulation of this receptor center may be via one of the known effects of thyroxine in vitro, the uncoupling of oxidation and phosphorylation. The chemical supposedly released by the hypothalamic center to stimulate the anterior pituitary has not been identified. TSH is a specific glycoprotein and has been prepared in relatively pure form by column chromatographic methods.[37] It must be noted that (1) plasma thyroxine may have a direct action on pituitary TSH production, and (2) the pituitary probably has a basal level of TSH secretion independent of hypothalamic control. Although the pituitary-thyroid axis seems well established in normal physiology, its relationship to hyperfunction of the thyroid gland is not at all clear. Suffice it to say that clinical evidence has not yet proved hyperpituitarism is present in Graves'

disease,[38,39] and that studies using presently available rough bio-assays for serum thyrotropin levels are inconclusive.[40]

A low level of thyroid activity seems to correlate with decreased adrenal activity.[41] It is not clear whether adrenal steroid production is increased or decreased in hyperthyroidism.[42] There is good evidence that increased plasma steroid concentrations decrease thyrotropin release and thus cause decreased thyroid activity.[43] Such a phenomenon is observed frequently in patients treated with large rations of steroids. The latter fact is part of the conflicting evidence cited in support of the theory that formation of thyrotropin and ACTH is reciprocally related.

Pregnancy or administration of estrogen is associated with stimulation of the thyroid and possibly increased production of thyroid hormone. Evidence suggests this stimulation is not mediated via the pituitary.[44] Estrogen also increases serum levels of TBP.[27] Perhaps this increase in TBP is a physiologic barrier serving to protect the fetus from increased plasma thyroid hormone by keeping thyroxine bound in plasma. The relationship of testicular hormones to thyroid function is not well defined, although depression of PBI can be produced by testosterone administration.[45] Stress and cold exposure cause thyroid stimulation via the pituitary.[46,47]

Relationship of Various Chemicals to Thyroid Function

An iodide-deficient diet leads to decreased hormone synthesis and, through pituitary thyrotropic secretion, to compensatory thyroid stimulation.[48] Unusually high doses of iodide block organification of iodide in the gland[49] and can cause hypothyroidism in rare patients. This problem has been noted in patients being given potassium iodide for a respiratory disease.[50] The marked amelioration of the symptoms of thyrotoxicosis produced by iodide ingestion has not been explained. High plasma iodide levels may inactivate thyrotropin;[51] inhibit organification, as just noted; or, by inhibiting thyroglobulin protease,[52] decrease thyroxine release.

KSCN and $KClO_4$ prevent trapping of plasma iodide by competitive inhibition[53] and thus decrease hormone production. The actual biochemistry is not known. The inhibition of the iodide trap by these anions can be overcome by raising the plasma iodide level.

The antithyroid drugs, propylthiouracil and methimazole, allow trapping of iodide but prevent its oxidation and organification[54] through an unknown mechanism, thus preventing formation of thyroid hormone. It has been suggested that these drugs reduce previously oxidized iodine back to iodide, or perhaps inhibit iodide oxidation by competitively blocking the oxidative enzyme system. It is of interest that thiouracil is incorporated into ribose nucleic acid in plant viruses in place of uracil,[55] and subsequently disrupts the ribose nucleic acid reduplication. However, several considerations suggest that this is unrelated to the therapeutic effect that these compounds have in hyperthyroidism.

Dinitrophenol, which uncouples cellular oxidation and the formation of high-energy phosphate bonds, also depresses thyroid activity.[56] It may be that this compound mimics the action of thyroxine at the hypothalamic receptor center and is "misinterpreted" as thyroxine. Its presence would thus lead to a decrease in thyrotropin release.

In certain instances, cobalt seems to act on the thyroid in roughly the same manner as thiouracil.[57] It can induce goiter and hypothyroidism.

Thyroid and Exophthalmos

For many years it has been known that administration of thyrotropic hormone to a guinea pig would cause exophthalmos. It is presumed that this phenomenon is related to the exophthalmos seen in Graves' disease. Histologically, the orbital changes in Graves' disease are characterized by an increase in orbital tissue fibroblasts and mast cells, edema and lymph cell infiltration of the extraocular muscles, and an increase in the amount of ground substance composed of hydrophilic hyaluronic and chondroitin sulfuric acids.[58] Subsarcolemmic, crescent-shaped deposits of mucopolysaccharides have been recently detected in the extraocular muscles in this con-

dition.[58] The same increase in mucopolysaccharides has been demonstrated in the skin in myxedematous patients and in the localized myxedema of Graves' disease.

Some experimental work suggests that a pituitary exophthalmos-producing substance can be separated from thyrotropic hormone, and that the two fractions are distinct entities.[59] At present, interpretation of this problem is subject to confusion because of a large amount of conflicting data. For instance, it has been demonstrated that an apparent exophthalmos can be produced in rats by administering cortisone.[60] Using the test animal in which the exophthalmos-producing substance was originally assayed, another investigator[61] recently demonstrated that exophthalmos can be produced by the administration of thyroxine.

In humans there is some suggestive evidence that exophthalmos is related to the increased level of thyrotropic hormone secretion. Hypophysectomy and radiotherapy directed to the pituitary region can apparently decrease malignant exophthalmos,[62] presumably by decreasing thyrotropin secretion. Exophthalmos is often accentuated in Graves' disease after thyroidectomy, when an increase in TSH titer might be suspected.

Locally injected tri-iodothyronine has been reported to diminish pretibial myxedema, a process[63] possibly related to exophthalmos. This evidence supports an alternative concept: Exophthalmos and localized myxedema may be a strange form of local hypothyroidism.

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Diagnosis of Tuberculosis

X-ray

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Tuberculin Testing

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Statement by Dr. Novak:

TUBERCULOSIS control is predicated on the fundamental concept of case finding; all the cases not only must be found but they must be found in an early stage. Thus, we have an opportunity actually to cure the patient, and, better yet, we find the patient in whom, by virtue of limited damage, there exists no opportunity to spread this disease.

There is actually one method by which a positive diagnosis of tuberculosis can be made and that is the demonstration of live tubercle bacilli in the sputum. This can be accomplished by staining a concentrated smear, finding acid-fast bacilli and growing the tubercle bacilli on culture or inoculating guinea pigs with the suspect material.

However, we have diagnostic weapons which

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are only presumptive in character. The tuberculin test is such a tool. It is a fine screen which indicates whether or not a patient has been infected with the tubercle bacilli. A positive test tells us only that the reactor has been infected. The test does not indicate whether clinical tuberculosis is present or will develop in a patient, nor does it presume that it will develop. The only information we gain is that the patient has been infected. Should the patient have a negative tuberculin reaction, we can safely say that at the present time he is free of tuberculosis infection.

A roentgenogram of the chest is also a tool which gives us only presumptive evidence of tuberculosis. The chest and the lungs are peculiarly adapted to roentgenographic inves-

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tigation. The relationship between solid tissue and air gives a beautiful contrast. A change in these relationships indicates changes occurring in lung tissue. Unfortunately, these changes are not specific for any one disease. They can occur in the presence of tuberculosis; bronchial, blood and vascular disease; foreign material, malignant and benign growths, and congenital defects. The roentgenologist can make only a presumptive diagnosis; other tests must be done to corroborate the diagnosis. What, then, is the advantage of a chest roentgenogram? It has long been demonstrated that if we wait for the patient to have the symptoms caused by lung disease we will find tuberculosis in a far-advanced stage. The shadows of tuberculosis can be found in the chest roentgenogram long before any symptoms are apparent to the patient. Thus, by employing the x-ray in potential cases, we will find presumptive tuberculosis in apparently healthy patients.

Our primary aim in making a roentgenogram of the chest should be to investigate those persons who are really potential cases of tuberculosis. Since tuberculosis is rarely found in persons from 2 to 14 years of age, it is useless and expensive to x-ray them. After puberty, the incidence of tuberculosis steadily increases; therefore, an x-ray of the chest should be done only in older individuals.

Not all communities have the same incidence of tuberculosis. In big cities, with their slum areas, it is much higher. Even in large cities there are special areas where tuberculosis predominates. Thus, the routine chest x-ray is definitely indicated in areas of increased incidence and morbidity. Is this true for suburban areas? There are many localities where the incidence of tuberculosis is very low. In these communities, we can find the potential case by using our fine screen, namely, the tuberculin test, and then x-ray the positive reactors.

Immediately the thought comes to mind that everybody is infected with tuberculosis when he reaches adult life. This was true about 40 years ago, but is not true at present. There are communities which are almost entirely free from tuberculosis infection. Therefore, it is evident that there are communities in which only 25 per cent of the people are infected. In such communities, it would be wise first to test with tuberculin and then to x-ray the positive reactors. In groups in which 50 per cent or more are positive reactors, routine chest x-rays of all members of the community are desirable.

Where are the groups with high tuberculosis rates usually found? Normally, the higher rates are found in (1) patients in general and mental hospitals; (2) recipients of public assistance, e.g., permanently and totally disabled persons, incapacitated parents of dependent children, the aged—especially those in geriatric hospitals, and single men living in lodging houses and cheap hotels; (3) members of racial groups and low-income families living in slum areas; and (4) inmates of penal institutions. A routine chest x-ray of the members of these groups is not only desirable, but it is important that it be done.

Briefly, it can be stated that the idea of conflict between tuberculin testing and the routine chest x-ray is more imaginary than real. In certain areas it is better to use the latter. Since the diagnosis of pulmonary tuberculosis is far from simple, especially in its early stages, both the tuberculin test and the x-ray, which complement and supplement each other, should be employed.

Statement by Dr. Lichtenstein:

THE tuberculin test is more valuable in the diagnosis of tuberculosis than is the x-ray because: (1) It is the only test which will clearly separate those persons infected with tubercle bacilli from those not infected. (2) It enables the approximate date of infection to be discovered by serial testing. (3) It makes possible the early treatment of infected persons so that serious complications are minimized. (4) It can be used to select persons eligible for BCG vaccination and to indicate whether a "take" has occurred after vaccination. (5) It excludes the diagnosis of tuberculosis. (6) It reduces radiation exposure.

General Considerations

To understand the potential usefulness of tuberculin testing, it is necessary to know cer-

tain basic facts about tuberculosis. The tuberculin reaction is negative in all persons until the first infection with tubercle bacilli occurs. It then turns positive, in 3 to 12 weeks, and generally remains positive for the remainder of the person's life. The first infection with tubercle bacilli causes the primary complex, i.e., childhood type of infection, which usually consists of a peripheral pulmonary tubercle of microscopic size with involvement of the local lymph nodes. About 97 per cent of children with primary infection recover without any evidence of clinical illness. The other 3 per cent have varying degrees of illness.

The first two years following primary infection are a period of danger. During this time, progression of the pulmonary lesion may occur, or miliary or meningitic complications dangerous to life may develop. Treatment with isoniazid begun at the time of primary infection will prevent or minimize complications. It is indicated particularly for infants and persons liable to frequent re-exposure to tubercle bacilli.

Healing of the primary infection requires a few months to two years and is accomplished through localization and walling off of lesions. Living tubercle bacilli usually remain in these so-called healed lesions. Thus, the patient has been vaccinated and has resistance to the disease in the vast majority of cases, as is shown by the fact that clinical disease develops in only a very small percentage of those infected. However, the presence of living tubercle bacilli in the patient constitutes a threat to his health throughout the remainder of his life. In periods of lowered resistance, proliferation of bacilli (endogenous exacerbation) can cause clinical disease.

At present, it is estimated that one-third of this country's population is tuberculin-positive and therefore has been infected with tubercle bacilli, and that two-thirds are tuberculin-negative and therefore have not been infected as yet. Because exposure to tubercle bacilli is becoming progressively less, our future population will contain a greater number of persons who are tuberculin-negative. This means that the test will become more valuable in the future. After the patient converts to a positive tuberculin reaction, the test is no longer of value, and he must be watched for possible development of clinical tuberculosis, i.e., reinfection tuberculosis, by means of x-rays at appropriate intervals.

Management Before and After Infection

Ideal medical management would consist of tuberculin tests at suitable intervals from birth onward until the conversion from negative to positive has occurred, followed thereafter by x-rays made at set intervals. Every physician should have pertinent records available on all persons under his care. As soon as the patient converts to a positive reaction, the physician should consider carefully whether treatment is indicated. Isoniazid will be valuable, particularly for infants, adolescents, personnel of general, mental and tuberculosis hospitals, prison personnel, and other persons who are likely to be exposed repeatedly. The remainder should be followed by serial x-rays, and, if a lesion develops, should be treated.

Tuberculin surveys—In surveying large groups for clinical tuberculosis, the tuberculin test can be used as a screening method. Those persons who are negative have not been infected and therefore need not be examined roentgenographically. Positive reactors can be x-rayed for evidence of a pulmonary lesion. This reduces radiation to the group and, in many instances, reduces the cost of the survey.

Tuberculin for BCG selection—Because BCG vaccine can be given only to those who are tuberculin-negative, it is necessary to use the tuberculin test to discover the persons suitable for vaccination. Those receiving the vaccine should include infants and adolescents from the lowest social and economic levels, particularly members of the nonwhite races; employees of hospitals, mental and penal institutions; medical personnel, and persons unavoidably exposed to tuberculosis in the family. The tuberculin test, therefore, is essential in the use of BCG vaccine, both to select the group and to determine after vaccination whether a "take" has occurred.

Tuberculin for diagnostic exclusion—Among persons suspected of having tuber-

culosis on clinical grounds, the tuberculin test can be used as a method of exclusion. A negative test gives over 99 per cent assurance that the patient does not have tuberculosis. This is very helpful in the diagnosis of numerous pulmonary conditions.

Summary

The tuberculin test is more valuable than the x-ray because it is the only method which can (1) identify all persons who have been infected, and (2) determine in serial tests the approximate time of infection. Thus warned, the physician can prevent or minimize the complications of the primary infection by using isoniazid. He also will be alerted to the necessity of following the positive reactors by serial x-rays so that clinical tuberculosis may be detected early.

The test reduces radiation exposure, since it makes it unnecessary to use x-rays in survey work in two-thirds of the population. Secondly, it is essential in selecting candidates for BCG vaccination and in demonstrating a "take" after vaccination. The test also can be most helpful in excluding the diagnosis of tuberculosis.

As the percentage of nonreactors in the population increases, the tuberculin test becomes more valuable. Every physician should record the tuberculin status of all his patients, follow positive reactors by serial x-ray examinations, and give treatment when indicated. Tuberculin testing is indispensable in the medical management of our population.

Comment by Dr. Novak:

There is an old saying that "there is a time and place for everything." This is especially true when one considers whether to use the tuberculin test or the chest x-ray, or both. In groups in which there is a high incidence of tuberculosis and in which the tuberculin reacting rate is sure to be above 50 per cent, it is both costly and impractical to use the tuberculin test, followed by chest x-rays of the positive reactors. Since these conditions are found in groups of older men, the question of radiation plays a very minimal part in our consideration. When we wish to make a tuberculosis survey of an industry, it is important to keep in mind the factor of practicability. It certainly will be very difficult to get the cooperation of industry to use both procedures when we must inform the management that it will be necessary to see each worker three times: (1) when we do the test; (2) when we read the test; and (3) when we x-ray the positive reactor. In a straight x-ray survey, the worker is seen only once—when we x-ray him. In a large industry, this is a matter of thousands of man-hours of work away from the job.

One must keep in mind that a chest x-ray is unable to demonstrate microscopic infection. The tuberculin test certainly can accomplish this. A negative tuberculin test can rule out the possibility that a density on an x-ray film is due to tuberculosis.

To summarize, I would use the chest x-ray alone in high-incidence groups and in industry, and use the tuberculin test in schools and in groups having a low incidence of infection, i.e., groups in which the reaction rate is less than 25 per cent.

Comment by Dr. Lichtenstein:

It is evident that both the tuberculin test and the chest x-ray have areas of great usefulness in diagnosing tuberculosis. The wise physician will employ each method wherever it is applicable.

The tuberculin test is indispensable for use in infants and children, in schools and colleges, and in any group where the percentage of infected persons is low. The test reduces radiation exposure and the information obtained is valuable in BCG vaccinations, in treating infected persons so that complications are prevented, and in excluding a diagnosis of tuberculosis.

The x-ray is a most valuable tool in discovering cases of tuberculosis among the heavily infected portions of large city populations, and is a short cut toward diagnosing patients who have a pulmonary lesion visible on film.

The discriminating use of all available procedures is the basis of good medical practice. Appropriate use of both the tuberculin test and the x-ray is indicated to achieve the best results in the diagnosis of tuberculosis.

CLINICAL STUDY

An Evaluation of Buffered Versus Nonbuffered Acetylsalicylic Acid

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SALICYLATES from natural sources have been used therapeutically since the time of Hippocrates more than 2400 years ago.[1-5] First synthesized by the chemist Von Gerhardt in 1853, acetylsalicylic acid was introduced into medical practice in 1899 for the treatment of rheumatic fever. For more than half a century aspirin has been the most widely used drug in the world.

The most important therapeutic use of acetylsalicylic acid is as an analgesic for the relief of simple headache and of muscular and neuralgic pains of various origins. Pain of either local or widespread distribution associated with myalgias and arthralgias is effectively controlled, as is pain of visceral origin in some instances. It also has effective antipyretic, anti-inflammatory and antirheumatic actions. Extensive reports on acetylsalicylic acid and other salicylates are freely available in the literature including one monograph with 4000 references.[1-15]

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In spite of the fact that acetylsalicylic acid was one of the earliest drugs synthesized, many facts about it still elude us. The mechanism of its analgesic action is still essentially unknown, although many years of intensive research have given us many interesting facts and theories.

There have been many attempts to enhance the analgesic action of acetylsalicylic acid while at the same time preserving the accepted safety of the drug. There has also been the desire to decrease, if possible, the incidence of minor side reactions present in a small percentage of patients, particularly those requir-

ing prolonged administration. It has been contended that the addition of buffering agents to acetylsalicylic acid would modify many of the principal actions of the drug, particularly the speed of onset of analgesia and the incidence of stomach upset.[10-12]

The present study was undertaken to determine whether such an addition of buffering agents as commonly utilized does in fact improve the results, give the same results, or give less satisfactory results when compared with acetylsalicylic acid alone in the conditions for which it is commonly prescribed.

Material

The material consisted of two tablets which were grossly identical in physical characteristics. Each tablet contained 0.3 gm. (5 gr.) of acetylsalicylic acid, with or without buffering agents. The tablets with the buffering agents, containing 45 mg. aluminum glycinate (dihydroxyaluminum aminoacetate), 100 mg. magnesium carbonate and acetylsalicylic acid (BUFFERIN®),[9] were purchased on the open market and repackaged. Bulk acetylsalicylic acid (BAYER® aspirin) was specially pressed in such a way as to be indistinguishable from the other tablet. The drugs were packaged in coded bottles labeled "A" or "B."

Method

Modern medical research has evolved many useful and reliable laboratory and experimental human testing procedures in many fields of medicine. In general, study of the action of a drug in animals gives us preliminary evaluations. Tests on normal human subjects may have a crude correlation, but not necessarily, with animal data. The final and ultimate evaluation of drug efficacy and safety can be accomplished only when actual clinical conditions exist.

In the field of analgesic testing it is unfortunate that such sequence of procedural steps cannot be followed. The reasons for this are few and simple. Acetylsalicylic acid cannot be reliably demonstrated as an analgesic by any presently known experimental testing methods either in laboratory animals or in normal human subjects.[1,8] Investigators agree that it does not follow from this that acetylsalicylic acid is not an analgesic; rather, our presently known experimental and analgesic testing methods are grossly inadequate for this type of compound.[1] That acetylsalicylic acid is an effective analgesic for many types of clinical pain is the common clinical knowledge of all practicing physicians.[1-5,10-15]

The only method presently available and generally accepted for testing the analgesic action and the incidence of side effects with this type of compound is careful observation by competent clinicians treating sufficient numbers of patients with real clinical pain under carefully controlled conditions.

One cannot stress sufficiently the importance of adequate numbers of patients as well as the decreasing to a minimum the number of variables which are present under clinical conditions.

A study was initiated utilizing the double-blind technic wherein neither the administering physician nor the patient knew the identity of the analgesic administered other than by code. Where the pain persisted more than one day a crossover design was utilized. The use of placebos in a study of this type, which does not involve the therapeutic efficacy of the basic drug, is not indicated, since the two drugs (one of which is an accepted standard) were being studied solely for the purpose of comparison.

In all cases two tablets containing a total of 0.6 gm. (10 gr.) acetylsalicylic acid with or without buffering agents were given from the coded bottles "A" or "B" for relief of clinical pain every four hours as long as necessary. Half the patients got two tablets first from bottle "A" and half from bottle "B." The coded compounds were rotated every 24 hours. Thus, when possible, the crossover design was employed so that patients with pain persisting more than 24 hours got both tablets, and they thus acted as their own controls. The identity of the code was not broken until after completion of the study.

Results

Clinical studies were conducted on a total of 354 patients with real clinical pain at two

TABLE 1

BUFFERED VERSUS NONBUFFERED ACETYLSALICYLIC ACID; ONSET OF PAIN RELIEF IN 199 PATIENTS

TIME OF PAIN RELIEF IN MINUTES	ASPIRIN		BUFFERED ASPIRIN		CUMULATIVE PERCENTAGE	
	Number of patients	*Cumulative number*	*Number of patients*	*Cumulative number*	*Aspirin*	*Buffered aspirin*
5	1	1			0.6	
10	9	10	7	7	6	4
15	26	36	22	29	22	18
20	17	53	8	37	32	23
25	1	54			32	
30	45	99	48	85	59	53
35	1	100	1	86	60	54
40			2	88		55
45	9	109	12	100	65	63
60	10	119	11	111	71	70
90	3	122	2	113	73	71
120	5	127	6	119	76	75
Pain relief total	127		119		76	75
No relief	40		40		24	25
TOTAL*	167		159		100	100

*One hundred and twenty-seven patients received both drugs in a crossover; 40 and 32 patients respectively received only one of the coded drugs; 326 recorded administrations of the drugs in 199 hospitalized rheumatic or arthritic patients (Hospital No. 1).

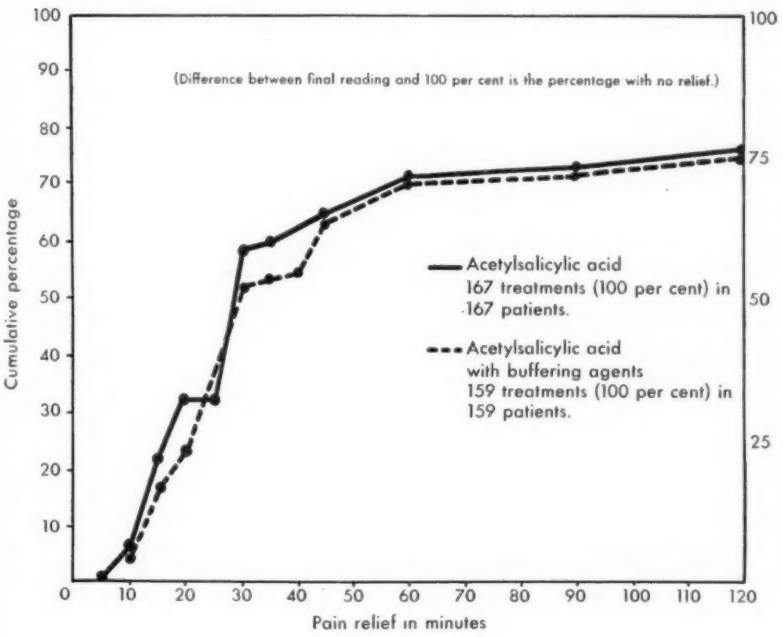

FIGURE 1. Graph showing the onset of pain relief in 326 recorded administrations of aspirin and buffered aspirin to 199 arthritic and rheumatic patients who were hospitalized.

different hospitals. The first group consisted of 199 rheumatic and arthritic patients and the second 155 patients from the medical and surgical services of a general hospital. Results were recorded and compared to see whether these two slightly different groups of patients taking salicylates—one with primarily static pain and the other nonstatic pain—had any clinically detectable difference in response to the two drugs.

Observations on each patient were recorded regarding (1) time of onset of pain relief, (2) degree of pain relief (complete, moderate, mild or none), (3) duration of pain relief (time when pain returned), and (4) side effects.

Since the administering physicians assumed that they were working with two different analgesics, there was considerable challenge to their diagnostic acumen to recognize any difference, however slight, between the two coded compounds in the light of the aforementioned criteria.

Hospital No. 1—The first group of 199 rheumatic or arthritic patients had the types of primarily static pain known to respond to salicylate therapy. In addition to their basic condition, they were treated for simple headache or for muscular and neuralgic pains. They ranged in age from 23 to 72 years.

The time required for the onset of pain relief is shown in both tabular and graphic form (table 1 and figure 1). Results with the two coded compounds were indistinguishable with regard to the time of onset, the effectiveness, or the duration of pain relief. The failure ratio and the incidence of side effects were likewise clinically indistinguishable.

Hospital No. 2—The second group consisted of 155 patients who were studied for relief of primarily nonstatic acute and subacute clinical pain on the medical and surgical services of a general hospital. They were treated for the various types of pain typified by simple headache or by the mild to moderately severe pain of bone, muscle or visceral origin. Approximately equal numbers of males and females varying in age from 20 to 65 years were in this group. Similar analyses regarding the aforementioned criteria—onset, effectiveness, and duration of pain relief as well as incidence of side effects—showed the two coded compounds to be indistinguishable.

A further analysis was made in this second group of 155 patients of the three basic types of nonstatic acute and subacute pains—headache, bone and muscle, or visceral—to see whether any difference between the two compounds could be distinguished (table 2). The average speeds of onset for the relief of the three basic types of pain studied clinically were not detectably different.

Incidence of side effects—A double-blind comparison of the two coded compounds in the 354 patients comprising the two groups studied regarding the incidence of side effects

TABLE 2

BUFFERED VERSUS NONBUFFERED ACETYLSALICYLIC ACID; TYPE OF PAIN AND ONSET OF PAIN RELIEF IN 155 PATIENTS

TYPE OF PAIN TREATED	ASPIRIN		BUFFERED ASPIRIN	
	Average relief in minutes	*Number of cases*	*Average relief in minutes*	*Number of cases*
Headache	15	36	15	41
Bone and muscle	23	41	25	38
Visceral	21	40	26	42
Pain not relieved		4		5
TOTAL*		121		126

*Ninety-two patients received both coded drugs in a crossover; 29 and 34 patients respectively received only one of the drugs; 247 recorded administrations in 155 patients on the medical and surgical wards of a general hospital (Hospital No. 2).

TABLE 3

INCIDENCE OF SIDE EFFECTS IN 354 PATIENTS RECEIVING BUFFERED AND NONBUFFERED ACETYLSALICYLIC ACID

SIDE EFFECTS	NUMBER OF PATIENTS	
	Aspirin	*Buffered aspirin*
Gastrointestinal upset Crossover group (219 cases)		
Initiated with both drugs	4	4
Initiated with one only	1	1
Single administration (135 cases)		
Initiated with one only	4	8
Patients with side effects	9 (3%)	13 (5%)
Patients with no side effects	279 (97%)	272 (95%)
TOTAL TREATED*	288	285

*Hospital No. 1: 199 rheumatic or arthritic patients; Hospital No. 2: 155 medical or surgical patients in a general hospital; total, 354 patients in 573 recorded administrations.

shows that they are both equally well tolerated, and differences cannot be detected clinically (table 3). The slightly higher percentage of minor gastrointestinal upset with the buffered drug (5 per cent) as compared with aspirin alone (3 per cent) is not significant.

Discussion

Our results confirm several recent clinical and laboratory studies in many hundreds of patients showing that differences in onset, duration and effectiveness of clinical analgesia as well as tolerance for acetylsalicylic acid alone or with buffering agents are clinically indistinguishable.[13-15] One other study states that the buffered aspirin seems to be at least as effective and fast-acting as ordinary aspirin.[11]

Batterman[13,14] analyzed the plasma level of free and total salicylates after oral administration of two tablets of each of the coded drugs, drawing samples at intervals of 0, 10, 15, 20, 30, 60 and 120 minutes. Salicylates were determined by three standard methods including total and free plasma salicylate determinations. No statistical differences were demonstrated between the two agents studied regarding blood salicylate levels. Cronk[15] analyzed salicylate acid blood concentrations in 20 patients after the administration of two tablets of both products. Results were essentially identical. These two investigations do not confirm Paul's[7] findings in a study of the salicylate blood level in which analyses were made at only the two intervals of 10 and 20 minutes; Paul reported higher levels for the buffered product. His article did not compare the analgesic actions of the two drugs.

Regarding the incidence of intolerance to the two compounds, our study in 354 patients confirms the observations of Batterman[13,14] and Cronk[15] that the rates of occurrence of minor intolerance to the two compounds are clinically indistinguishable. All these studies were done with single or double-blind technics with crossover studies when possible.[13-15] Paul and associates,[10] Tebrock[11] and Fremont-Smith[12] reported on the tolerance of the two compounds; they did not utilize the single or double-blind technics, but compared a history of intolerance to aspirin (this of course represents many years of taking aspirin alone) with the recorded intolerance to buffered aspirin primarily in short-term study. Under these uncontrolled conditions they reported better tolerance for the latter compound.[10-12] Tebrock[11] also reported on three patients intolerant to the buffered aspirin but tolerant to plain aspirin who were placed on an aluminum magnesium carbonate compound; all three noted mild reactions of nausea, indicating a possibility of drug intolerance or sensitivity to the aluminum in the buffering agent. Thus, the buffering agent per se can cause intolerance and sensitivity reactions.

While a history of intolerance is of interest, it is of questionable value in giving true comparative data. An illustration of this problem is reported by Cronk[15] in five patients who stated that gastric symptoms always followed the ingestion of unbuffered aspirin but never occurred after the ingestion of buffered drug. He administered acetylsalicylic acid in a tablet form identical with the buffered drug to these five patients in repeated doses without gastric

symptoms. This is one of the reasons why modern methods of study have evolved utilizing the single and double-blind technics for comparative studies.

In addition to the lack of clinically detectable better tolerance for the buffered compound, it is a fact that the buffering agents in the quantities present represent only a fraction of the minimal antacid dose as recommended in the U.S.P. or N.N.D.

It is concluded that the addition of buffering agents to acetylsalicylic acid serves no useful purpose detectable by either clinical or laboratory means presently available regarding either their analgesic actions or tolerance.

Summary and Conclusions

Coded compounds containing aspirin alone and aspirin with buffering agents were utilized in a double-blind crossover technic on static and nonstatic pain in several hundred patients.

These studies were carried out by two investigators so as to minimize the variation in evaluation. By the use of this technic it was found that there was no significant difference detectable under clinical conditions between these two agents regarding the following criteria: time required for onset of pain relief, analgesic efficacy, duration of pain relief, failure ratio, and incidence of side effects.

This lack of difference was particularly striking during chronic administration, where differences, if any existed, might be expected to appear.

It is concluded that the addition of buffering agents to acetylsalicylic acid in the concentrations used serves no clinically detectable useful purpose.

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CLINICAL STUDY

Improved Response in Angina Pectoris to a New Drug Combination

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MILTON PLOTZ

By far the most important group of drugs used for the treatment of angina pectoris are the nitrites, introduced by Brunton in 1867.[1] Nitroglycerin is the most effective agent in this group. It usually is used judiciously in conjunction with mild sedatives, and in the majority of patients it will control angina of effort sufficiently that they can live pleasantly and can resume work.

The nitrites relax smooth muscle; the effect is most marked in the finer blood vessels, especially in the coronaries, in which the dilation seems to last longer than in other vessels. The action of the nitrites appears to be independent of the nerve supply. All the vessels of the body take part in the vasodilation, with the most noticeable effect occurring in the postarterial capillaries. The nitrites increase the coronary blood flow in dogs by from 30 to 100 per cent.[2] The effect is striking and may be easily seen on the surface of the heart.[3]

White and Sharber[4] believed that nitroglycerin produced no increase in cardiac output, indicating that there was no direct effect on the myocardium. Wegria,[5] who found an increase in the cardiac output per minute, in the systolic output, and in the heart rate when there is no change in the blood pressure, concluded that while cardiac work is increased anginal pain is relieved, because the increase in coronary flow is relatively greater than the increase in cardiac work.

However, as useful as nitroglycerin is, it has several disadvantages, the most annoying being the speed with which its effectiveness is dissipated. Several other slower-acting nitrites have been tried in order to prolong the period

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of therapeutic action or to prevent attacks: inorganic compounds, such as sodium nitrite and bismuth subnitrate, and organic compounds such as mannitol hexanitrate. Most of these have been found to be of little use in treating angina pectoris,[1] although all liberate the nitrite ion in the body. Sodium nitrite may even have an adverse effect on cardiac pain in some patients.[6]

By far the most beneficial of the nitrite drugs is pentaerythritol tetranitrate. I have reported earlier on its value in reducing the dependence on nitroglycerin in angina pectoris, especially in angina decubitus and postprandial angina.[7] Subsequent experience has confirmed my first favorable impressions; others[8] have reported similarly. In one series,[9] this drug was found to be the most effective of several tested and seemed to be far more effective than triethanolamine trinitrite biphosphate in warding off anginal attacks.

Kissane, Fidler and Conn[10] found that the lowest death rate and the lowest incidence of thrombo-embolic complications in infarction occurred in patients receiving pentaerythritol tetranitrate. Some workers[11,12] have been unable to confirm these reported beneficial effects, but my colleagues and I find this drug to be the most useful of the slower-acting organic nitrites. Still others[13] found significant improvement in only 25 per cent of patients and equivocally favorable reactions in 55 per cent; however, since in 25 per cent of patients with angina, use of the drug might mean the difference between relative freedom from symptoms and a prolonged illness, these investigators concluded that it was worth trying.

Pentaerythritol tetranitrate should be given in 10 mg. doses, before meals. Patients who have nocturnal angina may take an additional dose before retiring. However, as pentaerythritol tetranitrate requires about half an hour for full action, combining it with nitroglycerin speeds the drug action and increases its effectiveness, especially if the dose is taken just before a meal or at bedtime. When this combination was first tried, 1/150 gr. nitroglycerin was incorporated, but it was soon found that 1/200 gr. sufficed in the majority of patients. When nitroglycerin is swallowed, the patient benefits from its prophylactic action, an action not fully appreciated by the majority of physicians.

It is often wise to combine the nitrites with a mild tranquilizer such as reserpine. Reserpine diminishes mild tension and edginess, moderately retards the tachycardia which often is found in subjects with angina, and slightly reduces hypertension if present. If the blood pressure is normal, reserpine has little effect on the blood pressure and may be safely given. Reserpine also is said to have some specific beneficial effect on angina pectoris.[14] A somewhat slower heart rate may bring about better coronary circulation by allowing more time for the ventricles to fill and more blood to be driven out of the left ventricle into the coronary vessels. The daily dose of reserpine exerting a mild tranquilizing effect is approximately 0.25 mg.

Clinical Study

Materials and methods—In a study to test the effectiveness of a new drug combination, a group of 106 patients with unequivocal angina pectoris started a two week course of Penite* therapy. In addition to rest, these patients required varying amounts of nitroglycerin each week. The most severe case of angina was in a patient who required about 80 tablets a week. All patients in the group had chronic coronary disease evidenced by either a documented history of myocardial infarction or clear-cut electrocardiographic changes. No patient with normal tracings or whose angina was not relieved promptly by nitroglycerin was included in the series. Six patients who started the experiment did not complete it for reasons irrelevant to the test.

Contraindications to the use of this drug were those which apply to the use of nitrates in general: severe anemias, glaucoma and cerebrovascular disorders.

Each tablet of Penite (test tablet) contains 0.3 mg. nitroglycerin, 10.0 mg. pentaerythritol tetranitrate and 0.07 mg. reserpine. In using the medication, the tablet usually is swallowed, but if more prompt action is de-

*G. W. Carnrick Company, Newark.

TABLE 1

RESULTS OF PENITE THERAPY IN 100 PATIENTS WITH ANGINA PECTORIS

RESULTS	DOSAGE OF NITROGLYCERIN *(Tablets per week)*	NUMBER OF PATIENTS	DOSAGE OF NITROGLYCERIN *(Tablets per week)*	NUMBER OF PATIENTS	DOSAGE OF NITROGLYCERIN *(Tablets per week)*	NUMBER OF PATIENTS	TOTAL NUMBER OF PATIENTS
Anginal attacks prevented or markedly reduced	Up to 10	30	10 to 20	41	21 or more	13	84
Discontinued nitroglycerin	Up to 10	24	10 to 20	21	21 or more	6	51
Need for nitroglycerin reduced to less than half	Up to 10	6	10 to 20	20	21 or more	7	33
Less pain, but nitroglycerin need not reduced to less than half; patients wished to continue test tablets	Up to 10	—	10 to 20	6	21 or more	3	9
Unsatisfactory results (no effect or made worse)	Up to 10	1	10 to 20	3	21 or more	3	7

sired, it may be taken under the tongue, where it quickly disintegrates. The drug should be administered only four or five times a day. If a patient requires only an occasional tablet of nitroglycerin, he may find the test tablet sufficient to abolish the need for nitroglycerin. Although this may mean a slight sacrifice in the speed of action, it eliminates the necessity of the patient's carrying two different medicaments with him.

In considering the procedure for this study of Penite therapy, we decided after some deliberation that a double-blind method of testing would be unsatisfactory. Thus, only enough test tablets were issued for a week's trial, and a placebo identical in appearance was used in either the first or the second week's trial. Sixty-nine patients were able to tell that the placebo was inert; 31 patients reported that the placebo was "much weaker," and none of the patients considered it more effective. In 50 patients, a comparison also was made between the test tablets and tablets containing 10 mg. pentaerythritol tetranitrate alone.

Reactions and results—Three patients complained of mild nausea but were able to continue using the tablet. Twelve were bothered by giddiness or lightheadedness. Only two patients discontinued using the drug. In 10 patients, the symptoms disappeared within a few days.

Forty-seven of the 50 patients to whom both the test tablet and the tablets containing 10 mg. pentaerythritol tetranitrate were given preferred the test tablet. Patients were especially gratified that this drug enabled them to prevent pain rather than to treat seizures. In practically every case in which the test tablet was effective, the patient has continued the medication since starting the test, a period now of a year or more. Results of the test, in which the patients swallowed a test tablet three or four times a day, are shown in table 1.

Summary and Conclusions

1. Nitroglycerin is the most effective short-acting drug, and pentaerythritol tetranitrate is the most effective longer-acting drug in the treatment of angina pectoris.

2. A tablet containing these drugs together with 0.07 mg. reserpine was used in 100 patients who had angina pectoris and who needed nitroglycerin for relief. Acute attacks were prevented or markedly reduced in 84 patients. In addition, anginal attacks were less frequent in nine patients. Therefore, favorable results were obtained in 93 per cent of patients, and over 50 per cent were able to discontinue the use of nitroglycerin entirely.

3. The action of a new combination of drugs (Penite) for the treatment of angina pectoris has been reported. It is a highly satis-

factory agent for the prevention of anginal attacks.

ACKNOWLEDGMENT

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1958

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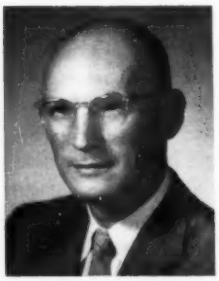
Psychosomatic Medicine and the Diagnostic Process

Much has been said about psychotherapy in medical practice. A much more fruitful approach is concern for diagnosis of emotional factors in illness. Prevalent medical attitudes and practices in diagnosis are more important in causing unsatisfactory handling of the emotional half of medicine than are limitations of the doctor's time and knowledge of psychodynamics. Specifically, the failure to clarify the patient's complaints is a common but unrecognized block to simplify diagnosis and treatment. This discussion will emphasize factors which tend to obscure understanding of the patient's complaints.



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HEMORRHAGE, SHOCK AND COAGULATION DEFECTS IN TERM PREGNANCY

Of all the causes of shock and hemorrhage which confront the obstetrician, those associated with defects in the mechanism of blood clotting are probably the most dramatic and the most terrifying. These defects can be associated with certain constitutional diseases, such as thrombopenic purpura, hypothrombinemia, pseudohemophilia, hyperheparinemia and hemolytic transfusion reactions. However, such complications are rare in childbirth; determining their causes, effects and management is a relatively empirical procedure.

Of particular interest to the obstetrician is the coagulation defect due to a diminution or lack of the fibrinogen content of the blood. This syndrome is known as hypofibrinogenemia or afibrinogenemia, depending on the fibrinogen level. Strangely enough, this syndrome has been described only within the last few years.[1] Since the condition is usually associated with alarming hemorrhage, it is interesting to speculate on why it was not recognized earlier. It seems reasonable to assume that the answer may well lie in the advances made in the technic of giving blood transfusions and in the maintenance of blood banks, which permit massive, rapid and safe transfusion of blood. Prior to the availability of these therapeutic weapons, the obstetrician was forced to watch his patient die of hypofibrinogenemia and its associated hemorrhage before he had a chance to investigate the cause or even to notice that the blood was not clotting.

The physiology and mechanism of blood clotting are most complex and still not completely understood. It is a matter of balance and counterbalance between the fluidity of the circulating blood and the stoppage of bleeding when a break occurs in the vascular system. Minute amounts of many interrelated and antagonistic substances are required for this intricate process. For the clinical purposes of this discussion a very curtailed schematic explanation of blood clotting may suffice: When there is bleeding from an injured blood vessel, the injured tissue pours forth thromboplastin. This reacts with prothrombin to form thrombin, which converts the fibrinogen of the blood into fibrin. The fibrin then combines with the blood platelets to form a clot at the

site of the injury. It would seem, therefore, that thromboplastin and fibrinogen are essential elements for the coagulation of blood and that an excess of thromboplastin could cause a deficiency in the blood fibrinogen by converting all or a great part of it into fibrin.

Afibrinogenemia or hypofibrinogenemia is usually associated with three well-known obstetric conditions: ablatio placentae, retention of a dead fetus for over a month, and amniotic fluid embolism. The condition also may occur immediately post partum in an otherwise apparently normal delivery. Placental tissue and amniotic fluid have a high thromboplastin content. Escape of such thromboplastic material into the maternal circulation will cause a depletion of fibrinogen, with resultant hemorrhage. It seems plausible that the open maternal sinuses in ablatio placentae and gradual breakdown of placental tissue in a retained dead fetus, with absorption of thromboplastin into the maternal circulation, will result in the occurrence of hypofibrinogenemia. The explanation of this syndrome in amniotic fluid embolism with its high thromboplastin content appears self-evident. Considering the combination of uterine contractions and open maternal sinuses in the second and third stages of labor, it is not surprising that this condition can follow apparently normal deliveries; it *is* surprising, however, that it does not occur more frequently.

The possibility of hypofibrinogenemia should be considered in all cases of ablatio placentae, retention of a dead fetus, and postpartum hemorrhage. When time permits, a determination of the blood fibrinogen level should be done. The normal fibrinogen content of blood is 250 to 400 mg. per 100 ml. A level below 150 mg. is significant. In cases of ablatio placentae and postpartum hemorrhage, a simple clot observation test is sufficient for clinical diagnosis. This consists of merely observing the clotting time of 5 cc. of freshly drawn blood in a test tube. Failure to clot or a clotting time of over five to six minutes is sufficient evidence of hypofibrinogenemia. It is important to note not only the clotting time but also the character of the clot itself. Occasionally the blood will clot in apparently normal time, but the clot itself is very unstable and friable and will disintegrate in a short time. This observation is also indicative of a coagulation defect. The tests should be repeated at frequent intervals until a diagnosis is established or the case is otherwise resolved. There are many other methods of determining clotting time, such as the Schneider test, but the simple one described is adequate for clinical management.

Other physical evidence of hypofibrinogenemia includes bleeding from the gums, sites of venipunctures and injections, and wound edges. Marked ecchymoses, nosebleeds and hematemesis also have been observed.

The management of hypofibrinogenemia consists of adequate blood replacement by fresh whole blood transfusion and the intravenous administration of fibrinogen. Four to six grams should be given as quickly as possible and should be repeated if necessary until adequate clotting of blood and cessation of hemorrhage occur. Fibrinogen is commercially available at a reasonable price and also may be obtained from many local Red Cross blood banks. No obstetric service, regardless of size, can be considered adequate unless at least 10 gm. of fibrinogen is readily available to the delivery room.

Since the management of the obstetric conditions associated with hypofibrinogenemia frequently requires surgical intervention, such as cesarean section or hysterectomy, it is well to point out that it is mandatory to correct the coagulation defect before operation. As previously noted, patients who have this syndrome bleed from all open surfaces. Operative interference will only cause more hemorrhage and may have tragic results. The fibrinogen level of the blood must first be brought up to normal; definitive operative surgery then may be done. In cases of severe postpartum hemorrhage, specific treatment of the hypofibrinogenemia frequently will stop the bleeding and obviate the need for a hysterectomy, which usually is planned.

If postpartum hemorrhage occurs, of course, the obstetrician must be aware of the possibility of a coagulation defect and have the available means to treat it; however, he

also should remember that the chief causes of bleeding in term pregnancy are obstetric in nature and are usually due to relaxation of the uterus or to lacerations, or both, of the birth canal. When faced with a bleeding parturient, the obstetrician first should search for these factors.

It should be emphasized that the subject of coagulation defects is very complex.[2] This short discussion merely touches the high lights of the practical and clinical aspects which the obstetrician should know in order to be able to diagnose hypofibrinogenemia and to institute the proper therapy.

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THE FUTURE OF SPECIALIZATION

The study and practice of medicine now include some 50 medical specialties as contrasted with five or six in 1900 and not more than 20 in 1925. Conspicuous is the division of the specialty of surgery into such separate sections as oral, plastic, thoracic, cardiologic, neurologic, urologic, orthopedic, ophthalmologic and otolaryngologic surgery. Similarly, internal medicine is beginning to be separated into cardiology, gastroenterology, hematology, chest diseases, allergy and other branches. This segmentation of medical science results from the tremendous advance in knowledge, the development of special technologies and instrumentations, and the adaptation of hospital services to specific needs. With such specialization has come an increase in administrative problems, particularly in developing the team approach to the care of the individual patient.

In an address before the annual convention of the American College of Gastroenterology, Dr. Chester S. Keefer[1] discussed "Specialism in the days ahead." "Specialties," he said, "are born by the desire on the part of men to learn more and more about a subject as an intellectual pursuit. . . . The people benefit because specialists are applying their knowledge for the alleviation of human suffering." He predicts that specialism of all kinds will increase and that the specialty of gastroenterology will broaden and deepen. In view of the great speed of progress, he recommends that the specialist be prepared emotionally for each stage in advancement. In order to preserve and further the specialty in the days ahead, he said, "It will be necessary to preserve the imagination of youth, to encourage the cross-fertilization of all the disciplines in science and to avoid anger and resentment when your specialty is attacked, ignored or belittled."

Few physicians seem to be aware of the significant changes wrought in various specialties by the development of new methods and new knowledge. Syphilology, once integrated with dermatology, has ceased to be a specialty and indeed may well disappear. The effectiveness of prevention and treatment has diminished the importance of syphilis in all civilized nations. The use of antibiotic drugs has diminished greatly the incidence of otolaryngologic surgery. More and more dermatologic disorders are being treated by general practitioners because of the effectiveness of various new methods of treatment. The field of allergy is so thoroughly integrated with all of the various specialties in medicine that it may be difficult in the future to maintain allergy as a specialty.

As some specialties diminish in importance, however, new specialties arise. Less than a decade has passed since the time when surgery of the heart was a great adventure; today, cardiologic surgery is practiced wherever competent surgeons and adequate facilities are available. Similarly, such developments as bone, artery and eye banks indicate new fields of surgery from which great progress may ultimately ensue. Although much of pediatrics is still practiced by general practitioners, the specialty has grown in numbers and in significance, and pediatric surgery already includes considerable numbers of devoted prac-

titioners. The increasing numbers of the aged in our population have led to the development of the practice of gerontology. One wonders, however, whether or not gerontologic surgery will eventually parallel pediatric surgery, since the use of new methods of anesthesia, blood transfusion and biochemistry, and of the recovery room and other technics involved in surgery has made surgical procedures on the aged commonplace.

MORRIS FISHBEIN

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THE PREMARITAL BLOOD TEST

MANY physicians who have been in practice some 25 years remember the first steps in the conquering of syphilis. Such discoveries as the identification of the spirochete, the Wassermann test, Ehrlich's salvarsan, and the educational campaign which began in 1935 were fundamental to progress. Hardly 25 years have passed since the word syphilis began to be used in newspapers and periodicals, since the public began to be educated about the prevention of venereal disease, and since premarital blood tests were made compulsory. Connecticut adopted the compulsory premarital blood test in 1935. By 1945, legislatures in 30 states had enacted a compulsory law. The noncompulsory areas that still exist include Minnesota, Washington, Nevada, Maryland, District of Columbia, South Carolina, Arizona, New Mexico and Mississippi.

In 1943, Mahoney proved that penicillin could cure syphilis. Since then the mortality from syphilis in infancy has dropped steadily. During the period from 1910 to 1956 the infant mortality from syphilis dropped from 131.4 to less than 1.0 per 100,000 infants.

After reviewing such statistics as those here cited, Drs. A. W. Hedrich and Charlotte Silverman[1] have now proposed in the *American Journal of Public Health* abolition of compulsory premarital blood tests. They find from the statistical evidence that the mortality and morbidity from syphilis are not influenced greatly by the compulsory premarital blood tests. They attribute the decline to such factors as intensified case finding, widespread examination and treatment of pregnant women, and improved therapy with penicillin. They note that the cost of premarital blood examinations is a considerable factor. Assuming that 2.5 million persons marry annually and that there is a medical cost of $3.00 per person, the total cost of premarital blood tests exceeds $7.5 million annually, not including the administrative overhead charges. Moreover, although rare, occasional false positive reactions are found, and the social and family impact of a false label of syphilis may be shattering. Many organizations, such as the American Academy of Dermatology and Syphilology and the Conference of State and Territorial Epidemiologists, have begun to question the desirability of continuing compulsory premarital blood tests. The nine states which failed to enact such legislation have nevertheless had a continuous decline in incidence of syphilis comparable to that of the states which have such a law. Already premarital blood testing is revealing so few infectious cases of syphilis as to make it an unproductive method of case finding. Drs. Hedrich and Silverman conclude that compulsory premarital blood test laws may create more penalties than benefits for our population, and thus are no longer justified.

In view of the evidence that they present, those who continue to favor such legislation must come forth promptly with sufficient documentary evidence to sustain their own point of view.

MORRIS FISHBEIN

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1. McKenna, C. J.: Am. Pract. & Digest Treat. 6:417, 1955. 2. Moyer, J. H.: M. Clin. North America, March, 1957, p. 405.

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Pfizer

• NATIONAL DIAGNOSTOR

PURPOSE: To hold two diagnostic lamps and provide them with controlled power through retractable cords.
DESCRIPTION: The molded plastic housing has sockets which can hold an otoscope and an ophthalmoscope securely, yet handy for use. The unit also provides connectors for attaching other conventional diagnostic lamps. Reeling in and out automatically, the 7 ft. cords can be locked at any point along their length. After the unit has been turned on, the power going to each instrument is controlled separately by means of two illuminated dials. These are self-indicating, eliminating the conventional sweep-hand meter entirely. Neither instrument lamp actually goes on, however, until the instrument is lifted from its socket, and dropping the instrument back in its socket automatically turns off its light. The built-in controller provides full, safe power to all instruments simultaneously without possibility of overload. The unit is designed for the standard 115 V 50-60 cycle, but can be adapted by the manufacturer for other current supplies. A rubber flange on the base of the housing keeps it immobile when standing on a desk or table top. A plate for wall mounting also is supplied. The unit is available complete with instruments, without instruments or with adapters for instruments of other manufacture.
PRODUCER: National Electric Instrument Division of Engelhard Industries, Inc., Elmhurst, N.Y.

• DURA-TAB S.M. QUINAGLUTE
(Change in Name)

DESCRIPTION: Formerly known as Dura-Tab S.M. Quinidine Gluconate, this drug provides sustained medication for cardiac therapy.
PRODUCER: Wynn Pharmacal Corp., Philadelphia.

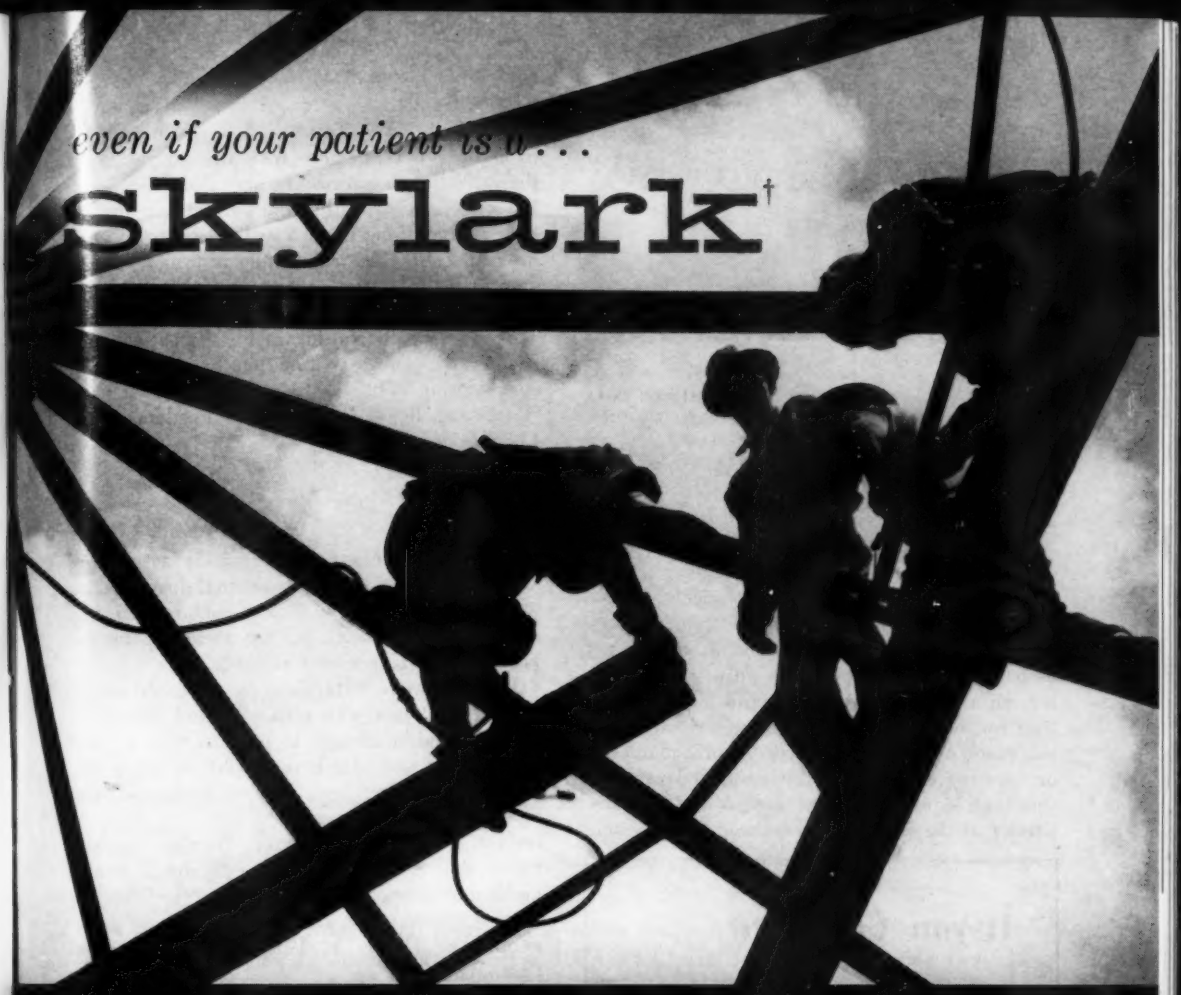
• POLYMAGMA® PLAIN

PURPOSE: Treatment of nonspecific diarrhea.
COMPOSITION: Each 30 cc. contains 3 gm. activated attapulgite and 270 mg. pectin in a special alumina gel.
DOSAGE AND ADMINISTRATION: For adults, 2 tablespoonfuls initially and 1 tablespoonful after each bowel movement until diarrhea is checked; for children, 1 or more teaspoonfuls.
HOW SUPPLIED: 12 fl. oz. bottles.
PRODUCER: Wyeth Laboratories, Philadelphia 1.

• STERILIZING UNIT

DESCRIPTION: Utilizing the bactericidal, virucidal and sporicidal properties of ethylene oxide, this portable, easy-to-use cold sterilizer requires no power source, will not cause sharp instruments to dull or rust, and will not damage sensitive materials. A Steribulb is placed in a piercing assembly, and the liberated ethylene oxide gas is then transferred to the aluminum sterilizing chamber which has a minimum volume of 1 l. and will hold 144 clinical thermometers. With a special extension, the sterilizer can be used for longer instruments such as cystoscopes. Made of ALCOA® aluminum, the unit weighs 3⅓ lb. It is especially suitable for critical lens systems or fine electric circuits. Although the gas in the Steribulb has a toxicity equal only to household ammonia, an activated carbon filter is fitted to the instrument's cover as an added safety feature.
PRODUCER: Ben Venue Laboratories, Inc., Bedford, Ohio.

(Continued on page A-98)



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(†structural steel worker—construction workers' slang.)

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‡U. S. Patent Pending
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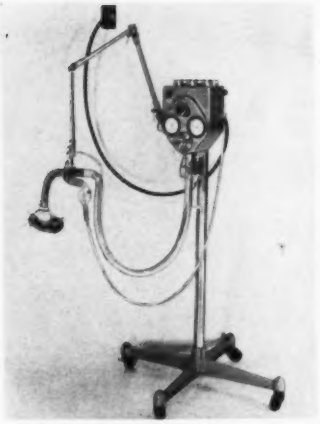

• **BENNETT PR-1A RESPIRATION UNIT**

DESCRIPTION: Designed for the clinical administration of intermittent positive pressure breathing in therapy, resuscitation or in respiratory assistance, this device has an adjustable aspirator, an air or oxygen diluter and a large nebulizer for long-term use. By a simple setting of an automatic cycling-rate control the unit maintains or insures respiration when employed as a resuscitator or respirator. Because of the flow sensitivity of the Bennett valve, the cycling mechanism does not interfere with the activation of the valve by normal respiratory effort. Even during automatic operation the patient can resume his own breathing pattern without being blocked or restricted. The respirator will again cycle automatically if the patient stops breathing or slows his breathing below the set cycling rate. This is especially significant for the patient who has some respiratory function but who is not coordinating well.
PRODUCER: Bennett Respiration Products, Inc., Los Angeles.

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• **SUITRATE**

PURPOSE: To provide antispasmodic action and sedation in treating gastrointestinal disorders.
COMPOSITION: Each milliliter contains 15 mg. sodium phenobarbital, 2.5 mg. methscopolamine bromide and 15 per cent alcohol.
CAUTION: May be habit-forming. It should not be given to patients with glaucoma and should be administered cautiously to patients with pyloric obstruction, prostatic hypertrophy or other urinary tract obstructions. The recommended dosage should not be exceeded.
DOSAGE AND ADMINISTRATION: Average maintenance dose for adults, 10 to 15 drops before meals and at bedtime.
HOW SUPPLIED: 4 oz. and 1 pt. bottles.
PRODUCER: The E. L. Patch Company, Stoneham, Mass.

• **IOCLIDE®**

PURPOSE: To destroy pathogenic microorganisms.
COMPOSITION:

Polyethoxypolypropoxypolyethoxyethanol-iodine complex	15.8%
Nonylphenoxypolyethoxyethanol-iodine complex	15.2%
(Provides 3.1% available iodine)	
Hydrogen chloride	0.20%
Inert ingredients	68.8%

DESCRIPTION: A concentrated, nonionic detergent, this disinfectant is stable and water-soluble in all concentrations, is nonirritating and nonstaining for most products, and is not affected by water hardness. It is effective against resistant strains of *Staphylococcus aureus;* spores; viruses, including polio types I, II and III; and bacteria, including tubercle bacilli.
PRODUCER: Clay-Adams, Inc., New York.

when you prescribe protection...

Consider her comfort. Women naturally welcome the comfort of the RAMSES® Diaphragm, with its cushion-soft rim, flexible in all planes to adjust to vaginal muscular action. The RAMSES dome, velvet smooth and thin, yet strong and durable, fits closely over the cervix to form a barrier against sperm.

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Consider the strength of motivation. Psychologic motivation has been found to be increasingly important to the success of contraceptive measures. So-called "method failures" may actually be "patient failures," the result of patients receiving inadequate information, underestimating the importance of the prescribed routine, or not sufficiently desirous of remaining nonpregnant. Properly used, RAMSES Diaphragm and Jelly reduce the likelihood of conception by at least 98%.[1]

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*Active agent, dodecaethyleneglycol monolaurate 5%, in a base of long-acting barrier effectiveness

1. Tietze, C.: Proceedings, Third International Conference Planned Parenthood, 1953.

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THE MEDICAL *Bookman*

► PRINCIPLES OF RESEARCH IN BIOLOGY AND MEDICINE

By Dwight J. Ingle, Ph.D., Professor of Physiology, The Ben May Laboratory for Cancer Research, University of Chicago, Chicago. 123 pages. 1958, J. B. Lippincott Company, Philadelphia and Montreal. $4.75.

Any student aspiring to attempt research should read this book. Any clinical pathologist who is carrying out a bit of clinical investigation should read this book. Any physician who thinks he has outlined a research problem, and can carry out a worthwhile study by writing request slips for work in a clinical laboratory, and can evaluate the results should read this book.

In other words, here is a book entertainingly written by a man who has devoted himself successfully to research.

The philosophy of scientific investigation, the use of statistical methods, and the interpretation of data are all presented in 11 chapters. After the introduction, follow chapters on limitations of mind, causality, probability, chance and "randomization," errors, heteropoietic factors, principles of testing, the experiment, interpretation of results, theory in biology and medicine, and relationships among scientists.

This may sound dry and stereotyped, but when you read the prologue and your eye is arrested by a sketch of G. K. Chesterton's "Father Brown," who was described at a distance as "a round dot which grew larger as it approached but did not change in shape," you realize that in this little book is something very different. In fact, there are so many apt quotations from Lewis Carroll and the immortal Alice and from many other philosophers that you are very apt to read the book through at one sitting. Then you will realize that at the end of each chapter there is a very complete bibliography of references that document the principles briefly discussed in the text of the chapter. One must discover this book for himself; and it should not be spoiled by attempting to review it, but I shall quote the following, which is anonymous:

> If you've got a thought that's happy,
> Boil it down.
> Make it short and crisp, and snappy,
> Boil it down.
> When your brain its coin has minted,
> Down the page your pen has sprinted,
> If you want your effort printed,
> Boil it down.

A. H. S.

► PSYCHOPROPHYLACTIC PREPARATION FOR PAINLESS CHILDBIRTH

By Isidore Bonstein, M.D. 143 pages with 16 illustrations. 1958, Grune & Stratton, Inc., New York and London. $2.50.

In slightly more than a hundred pages, Dr. Bonstein has succinctly outlined the various phases of painless childbirth. To achieve this approach, the discussion stresses, as have previous books on the subject, the necessity of education and activation rather than depression and inhibition of the psychic centers. The author emphasizes that psychoprophylaxis is totally different from hypnotism. He also analyzes the 10 to 20 per cent failures of the method.

Included are the texts used in a series of eight lectures in which the physiology of labor and of sensory perception and conditioned reflexes are discussed. The book is a well-written and concise treatise on painless childbirth.

E. A. B.

(Continued on page A-104)

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► THE POSTOPERATIVE CHEST
Radiographic Considerations After Thoracic Surgery

By Hiram T. Langston, M.D., Chief of Surgery, Anton M. Pantone, M.D., Radiologist, and Myron Melamed, M.D., Associate Radiologist, State Tuberculosis Sanitarium, Chicago. The John Alexander Monograph Series. 228 pages with 80 illustrations. 1957, Charles C Thomas, Springfield, Illinois. $8.00.

Included in this monograph are some 300 cases illustrating the many roentgenologic manifestations of usual as well as infrequent findings in the postoperative chest. These encompass both the uncomplicated and the complicated problems. The cases demonstrate not only the pulmonary but also the soft tissue, rib, mediastinal and diaphragmatic changes.

There is no text as such. Each case is illustrated with radiographic and pen-and-ink drawings which have brief explanations.

Residents in thoracic surgery or radiology may find this monograph useful, but its over-all value as a text for those practicing their specialties in active general hospitals is doubtful. Nevertheless, it does serve as a contribution to the memory of John Alexander, one of the great men in the establishment of the field of thoracic surgery.

S. B. F.

► INTESTINAL OBSTRUCTION

By Claude E. Welch, M.D., Clinical Associate in Surgery, Harvard Medical School, Boston. 376 pages, illustrated. 1958, The Year Book Publishers, Inc., Chicago. $10.50.

Written primarily for the clinical surgeon and the resident staff, this book presents a working outline and concept of the management of intestinal obstruction. The essential data presented in numerous key articles previously published, but not immediately available to the clinical surgeon, are consolidated in this text.

For the physician interested in the more detailed aspects of research in this field, the book is much too brief. The author apparently has not actually performed any significant amount of the basic investigation on intestinal obstruction, since he draws freely from the published work of others, some of whom have published books on this subject. However, the book is quite adequate for the clinical surgeon and the student, as it includes the essential features of the anatomy, normal and abnormal physiology, diagnosis, fluid and electrolyte management and treatment. Surgical technic is described briefly and is illustrated with numerous line drawings; statistical data are presented to emphasize the results attainable by various methods of treatment.

The author favors early surgical intervention in patients with intestinal obstruction, especially in those seen within 24 hours after onset of the obstruction, and he supports this thesis with statistical data. He stresses that intubation has a definite place in managing such patients, but warns against the false sense of security which intubation may provide. Various types of tubes are described and the contraindications to and the complications and effectiveness of intubation are well presented. Some of the major etiologic bases for obstruction are given, including inflammatory lesions, tumors, injuries, obturation, intussusception, volvulus, bands, hernias, megacolon, ileus and vascular lesions. The last chapter, a discussion of mortality due to intestinal obstruction, is an excellent summary of the literature and the effectiveness of our methods of treatment.

Y. S.

► VERTIGO AND DIZZINESS

By Bernard J. Alpers, M.D., Professor and Head, Department of Neurology, Jefferson Medical College, Philadelphia. 120 pages, illustrated. 1958, Grune & Stratton, Inc., New York and London. $5.00.

In this excellent and much-needed monograph, the author has presented the problem of vertigo and dizziness in a very practical and easy-to-understand manner. Approaching the often-baffling symptom of vertigo with logical reasoning, he has included discussions on the anatomic basis of the disorder, the labyrinth and its connections, the physiology of the vestibular system, mechanisms in the production of vertigo, associated symptoms and signs, and the causes, diagnosis and treatment. The material is presented concisely and pointedly and will be beneficial to all physicians, including surgeons, obstetricians, neurologists, otologists and general practitioners.

I. P. F.

(Continued on page A-106)

For high blood pressure, many physicians in Portland think of Serpasil first

Why? Because in Portland, Maine, as in most other places,* physicians know how versatile Serpasil is, how valuable it can be in almost every case of hypertension.

Serpasil may be prescribed in any of three basic clinical situations: *In mild hypertension,* Serpasil used alone lowers blood pressure safely and gradually, while calming the patient at the same time. *In more severe cases,* Serpasil is valuable as a priming agent to enhance the patient's response to more potent drugs. *In almost every case,* Serpasil used adjunctively lowers dosage requirements of other antihypertensive agents and thus keeps side effects to a minimum.

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***An objective survey of 1245 physicians in the U.S. and in 49 other countries brought out this fact: Serpasil controlled or helped to control high blood pressure in 73.8% of all patients treated.**

► SURGERY OF THE CHEST
A Handbook of Operative Surgery

By Julian Johnson, M.D., Professor of Surgery, School of Medicine and Graduate School of Medicine, and Charles K. Kirby, M.D., Assistant Professor of Surgery, School of Medicine, University of Pennsylvania, Philadelphia. Ed. 2. 398 pages with 86 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $9.75.

The fact that the second edition of this textbook follows the original by just four years is evidence of the rapid progress being made in this surgical specialty and is also an indication of the up-to-date information available in this atlas of thoracic operations. The details of operative technic are set forth in a straightforward and uncontroversial manner for each of the various useful and widely applied procedures employed by thoracic surgeons today.

Omission of all bibliography and reference to historical aspects has eliminated much cumbersome material. The section on heart surgery has been expanded to incorporate most of the technics presently of value in open-heart surgery. Considering the purposes for which this book was written, it would be difficult to identify any features subject to valid criticism.

This text should prove particularly valuable to the surgeon in training, for it provides a thorough yet concise introduction to the theory and practice of chest surgery.

D. C. M.

► POLYMYOSITIS

By John N. Walton, M.D., First Assistant in Neurology, University of Durham Medical School, King's College, Newcastle upon Tyne, England, and Raymond D. Adams, M.D., Bullard Professor of Neuropathology, Harvard Medical School, Boston. 270 pages, illustrated. 1958, The Williams & Wilkins Company, Baltimore. $7.00.

A worthy addition to the literature on muscular diseases, this monograph covers an uncommon disease in all its facets. There is an excellent review of the literature on the subject and a complete bibliography.

The book is written in the traditional style, initially covering the historical aspects in detail. It would have been helpful to have oriented the uninitiated reader by an early paragraph or two defining the current concept of this disease. However, the table of contents is an excellent outline of the monograph, and the reader can peruse the text in any order he chooses.

The authors report on their experience with 40 cases of polymyositis, 14 of which were in pure form, that is, involvement of muscles without associated skin or mesenchymal changes. Their clinical experience has been exceeded in number by previously reported series of cases. The discussion of the electromyographic changes in polymyositis is complete, although the experience of the authors in this regard apparently was limited. The clear and detailed discussion of the pathologic changes in the muscles, with the excellently reproduced photomicrographs, represents a major contribution.

J. P. W.

► HEMORRHAGIC DISEASES

By Armand J. Quick, M.D., Professor of Biochemistry, Marquette University School of Medicine, Milwaukee. Ed. 1. 451 pages with 37 illustrations. 1957, Lea & Febiger, Philadelphia. $9.50.

This monograph provides a comprehensive discussion of hemorrhagic diseases by a pioneer investigator and well-recognized contributor to our knowledge in this field.

The historical background of the various disorders is presented in interesting detail. Much space is devoted to considering current concepts of the physiology of coagulation and hemostasis and the disturbances believed responsible for bleeding disorders. The author's views concerning the many questions which remain controversial are presented fully, together with the laboratory technics on which he has based his conclusions. The bibliography in itself is extensive and valuable.

The clinical aspects of hemorrhagic diseases and the problems of management are given relatively less emphasis.

This well-written volume will be of interest to the student of hemorrhagic diseases and of value to the clinician seeking a degree of familiarity with recent progress in this field and an appreciation of the multiple diagnostic possibilities presented by the so-called bleeder.

T. C.

(Continued on page A-108)

80% of epileptics . . . can, with appropriate care and encouragement, lead a normal life"*

*Lord Cohen of Birkenhead: *British M. J.* 1:672, 1958.

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MEDICAMENTA VERA

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► PREVENTIVE MEDICINE FOR THE DOCTOR IN HIS COMMUNITY
An Epidemiologic Approach

By Hugh Rodman Leavell, M.D., Professor of Public Health Practice, Harvard School of Public Health, Boston, and E. Gurney Clark, M.D., Professor of Epidemiology, School of Public Health and Administrative Medicine of the Faculty of Medicine, Columbia University, New York, with 19 contributors. Ed. 2. 689 pages, illustrated. 1958, The Blakiston Division, McGraw-Hill Book Company, Inc., New York. $10.00.

Covering the field of preventive medicine most thoroughly, the authors and 19 well-known contributors have produced an excellent volume. They have also succeeded admirably in presenting their subject from an epidemiologic point of view.

Chapters are grouped into three sections: basic principles, application of principles, and public health—preventive medicine through organized community action. Numerous charts and diagrams give particular emphasis to and visual understanding of many parts of the text. The lists of references and suggested readings are helpful to the physician who wishes to read more about the subjects discussed.

If all physicians could and would take the time to employ the authors' philosophy in the promotion of health and disease prevention, we would certainly have a healthier nation. I recommend this volume to all physicians who wish to understand better the value and purpose of preventive medicine and how to approach the many problems in this field.

I. P. F.

Books received are acknowledged in this department. As space permits, books of principal interest to our readers are reviewed more extensively.

The Story Behind the Word. Some interesting origins of medical terms. By Harry Wain, M.D., Health Commissioner, Mansfield-Richland County, Mansfield, Ohio. 342 pages. 1958, Charles C Thomas, Springfield, Illinois. $8.50.

Manual of Medical Emergencies. By Stuart C. Cullen, M.D., Professor of Surgery and Chairman, Division of Anesthesiology, and E. G. Gross, M.D., Professor and Head, Department of Pharmacology, State University of Iowa College of Medicine, Iowa City. Ed. 3. 302 pages with 41 illustrations. 1958, The Year Book Publishers, Inc., Chicago. $5.75.

Clinical Enzymology. Edited by Gustav J. Martin, Sc.D., Research Director, The National Drug Company, Philadelphia. 241 pages, illustrated. 1958, Little, Brown & Company, Boston. $6.00.

Proceedings of the Sixth International Congress of the International Society of Hematology. Prepared and edited by the publications committee. 930 pages, illustrated. 1958, Grune & Stratton, Inc., New York and London. $25.00.

Fundamentals in Cardiology. By John B. Wild, M.D., Assistant Professor, Department of Internal Medicine, University Hospital, Iowa City. 83 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $4.50.

A Textbook of Psychology. By Donald Olding Hebb, Professor and Chairman, Department of Psychology, McGill University Faculty of Medicine, Montreal, Canada. 276 pages with 78 illustrations. 1958, W. B. Saunders Company, Philadelphia and London. $4.50.

A Practical Manual on the Medical and Dental Use of X-rays With Control of Radiation Hazards. By Richard H. Chamberlain, M.D. 31 pages, illustrated. 1958, American College of Radiology, Chicago. $0.25.

Dr. W. C. Röntgen. By Otto Glasser, Ph.D., Professor of Biophysics and Head, Frank E. Bunts Educational Institute, Cleveland Clinic Foundation, Cleveland. Ed. 2. 169 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $4.50.

Handbook of Treatment of Acute Poisoning. By E. H. Bensley, M.D., Director, and G. E. Joron, M.D., Assistant Physician, Department of Metabolism and Toxicology, The Montreal General Hospital, Montreal. Ed. 2. 212 pages. 1958, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $4.00.

A Therapy for Anxiety Tension Reactions. By Gerhard B. Haugen, M.D., Assistant Clinical Professor of Psychiatry, Henry Hadley Dixon, M.D., Head, Department of Psychiatry, and Herman A. Dickel, M.D., Associate Clinical Professor, University of Oregon Medical School, Portland. 110 pages. 1958, The Macmillan Company, New York. $3.50.

Alcoholism. By Arnold Z. Pfeffer, M.D., Director, Consultation Clinic for Alcoholism, New York University-Bellevue Medical Center, New York. 98 pages. 1958, Grune & Stratton, Inc., New York and London. $6.50.

Roentgenology of the Chest. Edited by Coleman B. Rabin, M.D., Attending Physician and Associate Radiologist for Chest Diseases, The Mount Sinai Hospital, New York, with 50 contributors. 484 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $19.50.

The Pasteur Fermentation Centennial 1857-1957. A scientific symposium with 20 participants. 207 pages. 1958, Chas. Pfizer & Co., Inc., New York.

Carbon Dioxide Therapy; a Neurophysiological Treatment of Nervous Disorders. Edited by L. J. Meduna, M.D., Professor of Psychiatry, University of Illinois College of Medicine, Chicago, with 18 contributors. Ed. 2. 541 pages, illustrated. 1958, Charles C Thomas, Springfield, Illinois. $14.50.

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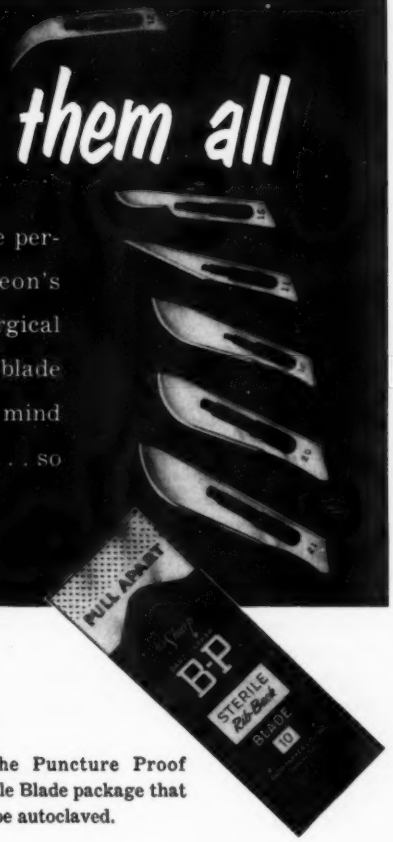

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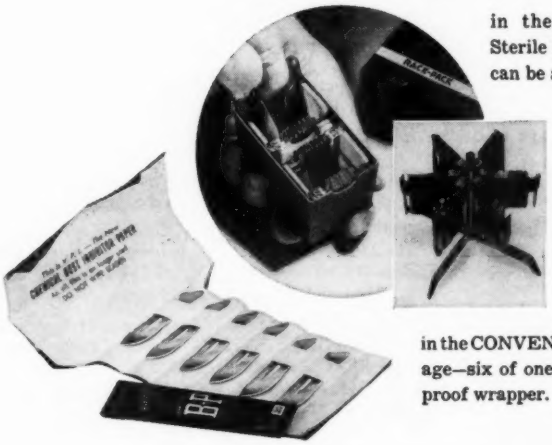

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News of Interstate

Scientific Exhibits, Demonstrations, Medical Movies Supplement Cleveland Assembly

SCIENTIFIC exhibits, medical and surgical movies, and teaching demonstrations will augment the outstanding teaching program of the Interstate Postgraduate Medical Assembly in Cleveland, November 10 through 13.

"Most physicians attending the four day Interstate meetings," said Erwin R. Schmidt, M.D., trustee and program chairman, "are seriously interested in learning as much as possible. We are, therefore, offering a wide selection of educational material, so that during intermissions and when lectures are presented outside of their special interests, they can visit the exhibit hall and secure additional instruction in the areas indicated."

The Cleveland Society of Pathologists will provide tissue demonstrations, while the departments of obstetrics and gynecology and orthopedic surgery of Western Reserve University School of Medicine present the other demonstrations noted. There will also be continuous showings of outstanding films supplied by the American Medical Association and by the American Cyanamid Company.

Schedule of Demonstrations

Monday, November 10

10:00 to 11:00 A.M.: Obstetric Manikin Demonstration—Allan C. Barnes, M.D., or associate, Western Reserve University

Tissue Demonstration of Cardiovascular System—Frederick W. Tillotson, M.D., Cleveland Society of Pathologists

3:00 to 4:00 P.M.: The Management of Colles' Fracture—Joseph E. Strong, M.D., Western Reserve University School of Medicine

Tissue Demonstration of the Endocrine System—John B. Hazard, M.D., Cleveland Society of Pathologists

Tuesday, November 11

10:00 to 11:00 A.M.: Obstetric Manikin Demonstration—Allan C. Barnes, M.D., or associate, Western Reserve University

Tissue Demonstration of the Respiratory System—Jerome I. Kleinerman, M.D., Cleveland Society of Pathologists

3:00 to 4:00 P.M.: The Management of Colles' Fracture—George Bennett, M.D., Western Reserve University School of Medicine

Tissue Demonstration of the Central Nervous System—Lowell Lapham, M.D., Cleveland Society of Pathologists

Wednesday, November 12

10:00 to 11:00 A.M.: Obstetric Manikin Demonstration—Allan C. Barnes, M.D., or associate, Western Reserve University

Tissue Demonstration of the Liver and Gastrointestinal System—Oliver Eitzen, M.D., and Eugene F. Koster, M.D., Cleveland Society of Pathologists

3:00 to 4:00 P.M.: The Management of Colles' Fracture—Joseph E. Strong, M.D., Western Reserve University School of Medicine

Tissue Demonstration of the Genitourinary System—Harold Gold, M.D., Cleveland Society of Pathologists

Thursday, November 13

10:00 to 11:00 A.M.: Obstetric Manikin Demonstration—Allan C. Barnes, M.D., or associate, Western Reserve University

Tissue Demonstration of the Breast—Edward Goodsitt, M.D., Cleveland Society of Pathologists

Financial Planning
for the Medical Practitioner

A monthly service dealing with the basic problems of increasing your net income and building personal capital . . . *in the face of today's high tax structure*

prepared by the

J. K. LASSER INSTITUTE

for

Postgraduate Medicine

AUGUST 1958

Care In Tax Matters - is important. Haste means more than waste. It can be costly in the form of tax dollars. Consider these two recent examples.

Forgetting To Sign Tax Return - held open taxpayer's return for assessment of additional tax. In his haste to file his tax return in time, a taxpayer mailed the return without signing it. After the normal statute of limitations for assessment had run, Treasury sought additional tax. The taxpayer claimed that regardless of the accuracy of his return, the statutory period for seeking additional tax had lapsed. But a court held the Treasury could properly seek additional tax on a return which had not been verified by taxpayer's signature. The normal statute of limitations barring additional assessment did not apply to an unsigned tax return.

Carelessness In Keeping Records Of Home Ownership - added to the real loss suffered by a couple as a result of fire casualty. Your home is a tax asset. If you sell your home at a profit, your gain is taxed as capital gain. You even can avoid taxable gain if sales proceeds are reinvested in a new home.

If you sell your home at a loss, no tax deduction is allowed for your loss. But that does not mean that losses arising from home ownership never give a tax deduction. If your home is damaged by casualty, you can deduct the loss in value up to, but not in excess of, your tax cost for the property.

A couple failed to keep records relating to the tax cost of their home, e.g., down payment, mortgage amortization, and capital expenditures. The home was destroyed by fire. An attempt to secure tax deduction for the resulting loss was denied. The couple could not show the tax cost for their home. And deductible loss cannot exceed such tax cost. In the absence of records which would put a ceiling (i.e., tax cost of the home) on amount of deduction, no deduction was allowed.

* * *

Will You Be Able To Retire - in comfort when you wish? Dr. B. L. Riese, when addressing the graduating class of Northwestern University School of Medicine some time back, pointed out that his own classmates ranged in age from 66 to 75 years. Of that group, "less than 30% (had) been able to retire." Dr. Riese's advice to those young physicians starting out in practice: Buy all the life insurance you can afford to carry in a sound company, and after taking care of insurance requirements, invest in sound stocks of basic industries. Leave the "gold mines to the gamblers."

Gear Your Insurance Buying For Dual Purpose - When your family is young and your children are growing, your primary aim in purchasing insurance is to furnish family protection in the case of your premature death. Per dollar coverage at younger age, term insurance will buy the greatest family protection. But term insurance does not build up permanent values. You cannot surrender term policies and receive cash surrender amounts. Ordinary life, 20-year and 30-year pay, do build up cash surrender values. When your family has grown and you have reached retirement age, you can surrender such policies for cash funds to provide retirement income for yourself and your wife. And the tax law now gives you a favorable election.

At the time of retirement, you can convert your life insurance policies to an annuity -- and make such conversion free of any tax. So cash values built up in life insurance policies can be transferred into an annuity -- without tax dilution which takes place on conversion of almost every other investment.

On existing policies that you own or policies that you contemplate purchasing, you might check with your insurance agent as to conversion features, keeping in mind the tax election now available.

How The New Annuity Rule Protects Retirement Income - You not only can convert your life insurance policies into annuity without tax under changed tax law, but on such conversion you also get additional tax protection. The method of taxing annuities has been changed favorably.

Assume that at time of retirement your life insurance policies have built up tax cost values of $40,000. You have a life expectancy of 10 more years. Suppose that on conversion of your life policies to an annuity, life insurance company will pay an annuity of $5,000 a year. On that annuity you'll realize taxable income of only $1,000 -- $4,000 of the $5,000 payment will be tax exempt. And that tax exemption continues for as long as you live. That favorable result is due to the new method of taxing annuities.

In the example, the doctor had tax costs of $40,000 tied to his life policies. At the time he converted such policies to an annuity, he had a life expectancy of 10 years more. By dividing the life expectancy of 10 years into the $40,000 amount, he arrives at an annuity exclusion of $4,000 a year. Only amounts in excess of that annuity exclusion are subject to tax.

Don't Ignore Inflation Peril In Your Retirement Planning - First National City Bank reports that over the last decade the dollar has depreciated at a rate of 2.2% a year. Even though attempts are being made to halt inflation, dollar depreciation is a factor which must be considered in any long-range investment program. The typical program involved in retirement planning is a long-range one. Taxes also add to the inflation threat.

Consider the successful doctor with taxable income over $35,000 a year. He invests surplus funds in a safe investment with little growth potential and reinvests investment return each year as a method of building up retirement capital. Due to the combined inroads of taxes and inflation, the doctor might find that after initial investment his capital would not increase in terms of purchasing power -- even though he reinvested his after-tax investment income in full. Here's why.

After taxes, investment return would be cut to a little over 2%. Inflation inroads would equal that return -- might even exceed it if rate of dollar depreciation accelerates. At time of retirement, the doctor would have greater amount of dollars invested in his retirement fund, but those dollars would have lost so much in purchasing power that they would buy no more than the original capital amount invested many years before.

In Selecting Stocks For Retirement Investment - concentrate on those which hold potential for greatest growth. Don't be misled into investing solely in the good dividend-paying stock because of the higher yield. A good dividend will be immediately depleted by tax due on it, and the stock paying the high dividend normally has a reduced growth potential.

If you invest blindly in sound companies, you'd probably find that growth potential of the companies selected would approximate the rate at which the dollar is depreciating. The average American company grows at a rate of close to 3% a year -- and that growth factor ultimately will be reflected in higher value for the company's stock. So if you invested in such a company, its growth factor would offset inflation. On reinvestment of investment return, you'd be building capital values for retirement. But some companies consistently have grown at a rate of around 10% or more. Investment in such a company would not only offset inflation, but would build

added retirement capital for you -- even though you did not reinvest current return on such investment. The big problem is to find the companies which grow at a faster rate than the average, with the resulting accelerated increase in stock values for your benefit.

Earnings Retention Companies Build Capital Values - These companies which retain a substantial part of earnings for business expansion hold the potential for accelerated increase in equity values. Two corporations are earning 8% after taxes. One pays out 75% of its earnings as dividends, retains only 25% for expansion. The other pays out 25%, retains 75%. If an investor in the 75% bracket invested $5,000 in each company and reinvested current return after taxes, what amounts would he have invested in each company at the end of 15 years? On the first investment, he'd have compounded equity values of less than $9,000. On investment in the earnings retention company, he'd have compounded equity values of $13,000. The difference in values is due to the fact that the bulk of earnings escapes a second current tax (i.e., tax on dividends received) when investment is in the earnings retention company. The spread in equity values would not be as great for an investor in a lower tax bracket, but there would still be an advantage resulting from investment in the earnings retention company.

Earnings retention ultimately will mean higher dividends, also. A brokerage house checked performance of a portfolio of earnings retention companies favored back in 1940. A $10,000 investment in such portfolio in 1940 would have grown to $73,000 by 1955 -- 15 years later. Based on market, the companies were still following an earnings retention policy, paying out only $1,540 in dividends. But those same dividends gave a yield of 15.4% on the original $10,000 investment.

Brokerage houses maintain lists of companies which follow a consistent earnings retention policy. The doctor who does not need investment return for current living needs might check for companies in various industries which follow this policy.

* * *

Doctor's Recommendation Allows Medical Expense Deduction - for tape recorder, special typewriter, projection lamp, and special lenses. Treasury is adopting a more liberal and realistic view as regards expenses connected with medical care, particularly for children. Here's a recent example.

A taxpayer's son suffered from an eye condition which ultimately would lead to blindness. In order to preserve his son's eyesight for as long a time as possible and yet permit him to continue his education, a doctor recommended purchase of a tape recorder, special typewriter, a projection lamp, and special lenses. The father was allowed to deduct cost of these as medical expenses.

Now available at cost—$1.50—3-ring loose-leaf binder to hold 24 monthly Lasser reports. Made of blue simulated morocco grain leather; non-soil finish with embossed cushion edge. Send check with name and address to POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

BREAKTHROUGH FOR THE PATIENT

Freed from the encumbrances of needle syringe and sterilization, and freed from the tensions caused by worry about potential hypoglycemic reaction, the patient on Orinase can look forward to a more normal type of life in which his metabolic disorder is not complicated by the paraphernalia of injection.

For the newly discovered patient, the diagnosis of diabetes is no longer a commitment to a long sentence of injections. Families of diabetics can now assume a more normal way of life, unimpeded by social and economic disabilities and the personal demands of the metabolic invalid. This new era has opened for the majority of diabetics. Those most responsive have had onset of diabetes after 40 years of age and, if on insulin, generally require less than 40 units daily.

BREAKTHROUGH FOR THE PHYSICIAN

"Orinase-responsive" patients, as a group, usually enjoy a superior quality of control. With Orinase, the management of diabetes is smoother, associated with a feeling of greater stability and well-being, and free from the danger of hypoglycemic shock. Patients are more cooperative and can assume occupations from which hormonal therapy might disqualify them.

New diabetics are easier to indoctrinate and to manage. Mild diabetics, who either personally object to insulin or whose diabetes is so mild as to make one hesitate to add insulin to the regimen, are both excellent candidates for Orinase.

BREAKTHROUGH FOR METABOLIC INVESTIGATORS

It has been shown that Orinase corrects hyperglycemia by stimulating the elaboration and release of *native* endogenous insulin. Its administration in the presence of functional beta cells results in changes in fat and protein metabolism known to be the physiologic resultants of insulin activity. More recently several investigations have demonstrated that the effects of Orinase upon hepatic glucose release are none other than those of endogenously produced or endoportally administered insulin. These observations have been followed by the further realization that the liver may play a primary physiologic role in the mechanisms of insulin action. Experience with Orinase suggests a classification of diabetics into two apparently distinct groups—the Orinase-responsive or the "Orinase-positive" diabetics and the "Orinase-negative" diabetics. It remains to be determined whether these will prove to be distinct clinical entities.

Upjohn

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

June 1—In New York only three hours late. By car to La-Guardia and off to Chicago on Capital Airlines, which flies British Viscounts. To dinner came all the grandchildren except the tiny new Ann Marie, and it made a great occasion.

June 3—On plane to Rochester in Minnesota and reading "Inside Russia," which has but little to say of medicine. At the airport Gus and Zelma Buie. So to lunch at the Kahler in the Hemisphere Room, now beautifully redone with a fine new addition. Here were Teresa Cohen and Sylvia Covet. So registered for the Medical Library Association and met Tom Keys, Scott Adams and Frank Rogers, but couldn't find San Larkey or John Fulton, whom I missed sorely. In the afternoon for tea to the Mayo Foundation House, where were all the lady librarians with Mesdames Balfour and Walters pouring. Here Mistress Pepys and the old gentleman reminisced of the olden days with Dr. Will and Hattie and all the distinguished guests who came there. Next to dinner at Michael's with the librarians of the pharmaceutical companies, who were multitudinously present, and after that to Plummer Hall where *Mademoiselle* Louise C. Lage of Eli Lilly introduced old Pepys most cleverly as if he were a pill, and he talked of indexes and bibliographies. Then Phil Hench gave a glorious lecture about Sherlock Holmes, illustrated with the trail of the great detective and his last struggle with the despicable Moriarity.

June 4—All the librarians off to Minneapolis and old Pepys under the guidance of Mr. Williams off on a tour through the new clinic building with its magnificent murals and examples of the ease of automation. At noon to luncheon with Don Balfour and Carrie and talking of the past and the future. In the afternoon to travel through the city, visiting the great IBM plant, where the accounting machines are assembled. Thereafter to visit the new International Motel, where all the rooms are of the different nations with maximum comfort and perfect décor. To dinner at the Kahler—one of the nicest ever, with marvelous steak. As guests of the Buies came Winchell Craig, Bill Braasch, Phil Brown, James Eckman, H. C. Habein, Phil Hench, Russell Wilder, Stuart Harrington, Herbert Giffin, George Eusterman and the ladies.

June 5—To the desk for my scrivening and for a long interview with chief editor Eckman. For luncheon at the Waltman Walters' along with Madame Estes from Texas. Thereafter to hear a symposium on medical history with Victor Johnson, Helen Clapesattle Shugg and Sister Mary Brigh, and the Sister captivated the audience by the sweet simplicity of her address. So with her to tour the hospital, seeing the new chapel, the intensive treatment center and the neuropsychiatric section, all lavish and superb, with the whole hospital spotless and the discipline of the best. At night to the banquet in the Elizabethan Room of the Kahler. Here four young medicos, G. A. Lillington, G. T. Ross, H. K. Ivy and P. F. Wilson, united in a barbershop quartet.

June 6—For two hours of conference on education with Victor Johnson. To luncheon at the Scandia in the Zumbro and met Roy Watson, who now manages the Kahler chain with the efficiency of a Hilton, and he reminded me that he had been in the graduating class when old Pepys was the speaker in 1939 and he told me what I said. In the afternoon again reading Gunther's "Inside Russia," the best of it being the perspicacious analyses of character. In the evening to dine with Robert P. Gage, president of the board of education, James V. Moon, superintendent of schools, Phil Brown and Willis of the school board and all the ladies. Then all to the Mayo Civic Auditorium, where old Pepys met a woman who was graduated in 1939, having been married two days previously, and her daughter, being graduated this day. And the damsel piped out: "Besides I'm getting married tomorrow." So old Pepys in his convocation address promised to come back in 1978 for the grandchild's graduation. The city of Rochester has a grand new high school with a great hall and this was the last graduation to be held in the Civic Auditorium.

June 9—Back in harness and a letter came from Herbie Cooper, enclosing some photostats of articles published long ago in the *Medical World*. A Dr. A. C. Gore of Hohenlenden, Mississippi, recommended rapid opening and

(Continued on page A-136)

WHY RISK DELAYED RECOVERY FROM

PYODERMAS?

Many of the organisms causing pyoderma are refractory to routine antibiotic therapy. If the offending organisms are resistant staphylococci, CATHOMYCIN (novobiocin) is indicated. CATHOMYCIN has an established record* of effectiveness against strains of organisms resistant to other antibiotics. It may be administered alone, or combined with other antibiotics for protection against the emergence of resistant strains.

Of particular value in hard-to-control pyodermas caused by resistant staphylococci, CATHOMYCIN is rapidly absorbed—producing therapeutic blood levels that last for 12 hours or more. The drug is generally well tolerated and there is no evidence of cross-resistance with other antibiotics.

CATHOMYCIN®

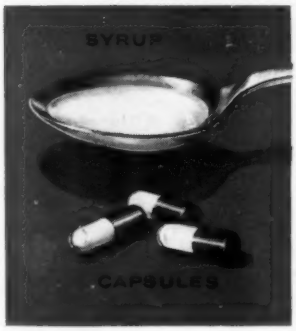
NOVOBIOCIN

for staphylococcic septicemia, enteritis, postoperative wound infections and other serious staph infections.

DOSAGE: Adults: CATHOMYCIN Sodium 2 capsules b.i.d. or CATHOMYCIN Calcium Syrup 4 teaspoonfuls b.i.d. Children: (up to 12 years) 2 to 8 teaspoonfuls daily in divided doses based on 10 mg. CATHOMYCIN per lb. of body weight per day.

SUPPLIED: Capsules sodium novobiocin, each containing the equivalent of 250 mg. of novobiocin—vials of 16 and 100—and as an orange-flavored syrup (aqueous suspension), in bottles of 60 cc. and 473 cc. (1 pint). Each 5 cc. CATHOMYCIN Syrup contains 125 mg. (2.5%) novobiocin, as calcium novobiocin.

*Complete bibliography available on request.



MSD MERCK SHARP & DOHME Division of MERCK & CO., Inc., Philadelphia 1, Pa.

shutting of an umbrella over a feverish patient to cool him off and to dispel fecal odors in the bedroom.

June 10—Now finished with "Inside Russia," and especially impressed by the vast improvement in education.

June 11—At noon came Dr. Phil Reichert and Faith to lunch and to talk of changes in the medical scene and of collecting diverse objects in which he and Mistress Pepys have both won repute.

June 12—By the early morning plane to Troy, New York, meeting Dr. Montague, Jay Gould and many science writers and editors with more than 30 medical editors, including Claire Schore from the Cancer Society, Maude Hulse of Quincy, Mildred Lysle of the Cleveland Clinic, Rita Chazan of the Buffalo Health Department. What a pleasure to lecture to such ladies. Also here were Carey of Lederle, Sturchio of American Cyanamid, Anzlowar, the learned Russian of Eaton, and Battista, Lutz and Ingram of Warner-Chilcott. So in the evening to the Troy Country Club for high festivities, and spoke again of medical progress.

June 13—Through three thunderstorms home on TWA. Immediately to the Chicago Lying-In Hospital for a cocktail party, where came the obstetricians from near and far to celebrate the opening of the new research center. Thereafter to the South Shore Country Club, where M. Edward Davis, Lowell Coggeshall and Allan C. Barnes were speakers. Dr. Barnes of Western Reserve told of "Perpetuation of errors," with startling effects on his audience.

June 14—At noon for luncheon in the hospital, speaking mainly with Paul Hodges of his new column in POSTGRADUATE MEDICINE. So then to the Dora DeLee Amphitheatre, where John L. McKelvey gave the Arthur Koff Memorial Lecture, telling that there is no physiologic anemia of pregnancy, and such as there is may be controlled by iron. Next George W. Corner told learnedly of American contributions to knowledge of the reproductive cycle and principally of the glandular products derived from the ovary. Dr. Nicholson J. Eastman of Hopkins considered "Trends in obstetric research" and C. Lee Buxton of Yale, "The future of obstetric care," and old Pepys duly noted the disappearance of the "al" ending from "obstetric." To conclude this great occasion came Donald H. Barron about the fetal oxygen supply which showed the deadly effects of insufficiency. In the evening to the Quadrangle Club for the communications dinner of the University of Chicago Alumni. Here Leo Rosten presided most cleverly as always. Clifton Utley awarded the prize to Miss Gordon, editor of *House Beautiful*. Mr. Shugg, formerly of Minnesota and now of the University of Chicago Press, described the great advances in university publication, and Sidney Hyman of the *Washington Post* discussed the sad state of a presidency with power but without influence. So took home Mrs. E. V. L. Brown and Mrs. Dallas Phemister, who gladdened these old eyes again, and also the Reicherts to their hotel.

June 16—This noon to the Standard Club for a meeting of the Scientific Advisory Board of the Municipal Tuberculosis Sanitarium. Ernest Irons reported on much progress and the need for additional facilities in the area of Provident Hospital. Here were new members Egdorf, William Adams, James Campbell, Clarence Jones, Herbert Longnecker and E. Lee Strohl.

June 17—By plane to New York, meeting with Warwick and MacDonnell. Thereafter with Soroko to Lindy's and then to see "Say, Darling," which is full of fun, but thought Johnny Desmond excellent.

June 18—To confer with Dr. Parmele and Lewis Gruber, whose company does well indeed. At noon came Peter Warren, Paul Robinson, Ellwood Douglass and Max Geffen to work on our new periodical. In the afternoon to see Milton Runyon and Doug Black at Doubleday. Next to meet Basil O'Connor and Mel Evans with Polly at the Forum and to see William Inge's wonderful play "The Dark at the Top of the Stairs."

June 19—Early to Morris Plains to meet with Elmer Bobst, Al Driscoll, Bill Lasdon, Len Scheele and the staff. Then driving back with Elmer Bobst to the National Hospital for Speech Disorders, where once presided James Sonnett Greene. Next came Clifton Cooper to talk of patents, and then to the Plaza for sherry and converse with Herbert Mayes. Still later, again to the Forum and afterward with the Runyons to see Lunt and Fontanne in a dismal offering called "The Visit," but their performances as always of the very best. And then to greet Sherman Billingsley at the Stork Club, the pickets still picketing, and here until late in joyful supper with Grace and Herbert Mayes.

(Continued on page A-138)

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Riboflavin (B_2)	12.5 mg.
Nicotinamide	50.0 mg.
Pyridoxine HCl (B_6)	3.0 mg.
Calc. pantothenate	10.0 mg.
Vitamin C (ascorbic acid)	250.0 mg.
Vitamin B_{12} with intrinsic factor concentrate	1/9 U.S.P. Unit

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June 20—Early to Lorillard and talked of cancer of the larynx. Then to lunch came Joseph Marks and Louis Berlin with his lady and Mermin and we talked of the launching of the Anne Frank Foundation. Now came Ed Pool, who would promote a new device for intradermal administrations. So drove to Scarsdale, where a great *fiesta* in a tent at the Lasdon domicile with all the family and a host of friends.

June 21—The rain continues to pour, so off at noon on the plane for Chicago and began at once on the piled-up desk.

June 22—To Ravisloe, playing at golf with Friedell and the ladies and somewhat improved. Discussed also with Maurice Goldblatt plans to build a surgical research pavilion at the University. And later watched the "$64,000 Challenge" and "What's My Line," and convinced there is some finagling in both to make a good show.

June 23—At the desk until noon and then to the CAA to meet with the board of Lyric Opera, hearing about Carol Fox's new baby girl and Marv Welfeld's new baby boy and about our new conductor, who also conducts for Van Cliburn, the pianistic phenomenon. Thereafter to H. Asher, the dentist, who can see no merit in Sherman Adams' alibi. Finished also Evans Hunter's novel "Strangers When We Meet," a tale full of passion and nymphomania and the intricacies of illicit love in the suburbs, most remarkable for the veracity of its dialogue.

June 24—Having read in the *Boston Medical Quarterly*, better known as the *B.M. Quarterly*, an editorial statement on writing which used the word "sculpt," wrote to Joseph Garland that I thought it obsolete and only used jocularly, but he said the writer was his son and that he felt as I did, and he finished poetically:

"Though devoted, since high as a knee,
To poetry and prose that is free,
On encountering 'sculpt'
I admit that I gulpt—
It's new to you, Webster and me."

To the Standard Club for dinner with five grandchildren and then all to see the White Sox play the Yankees, who made five runs including three home runs in one inning. Reading now "Discovering Ourselves," by Edward A. Strecker and Kenneth E. Appel, which makes modern dynamic psychology reasonably simple, and this new edition is even better than the one I first enjoyed in 1931.

RICHARD ARMOUR

ALL OFF

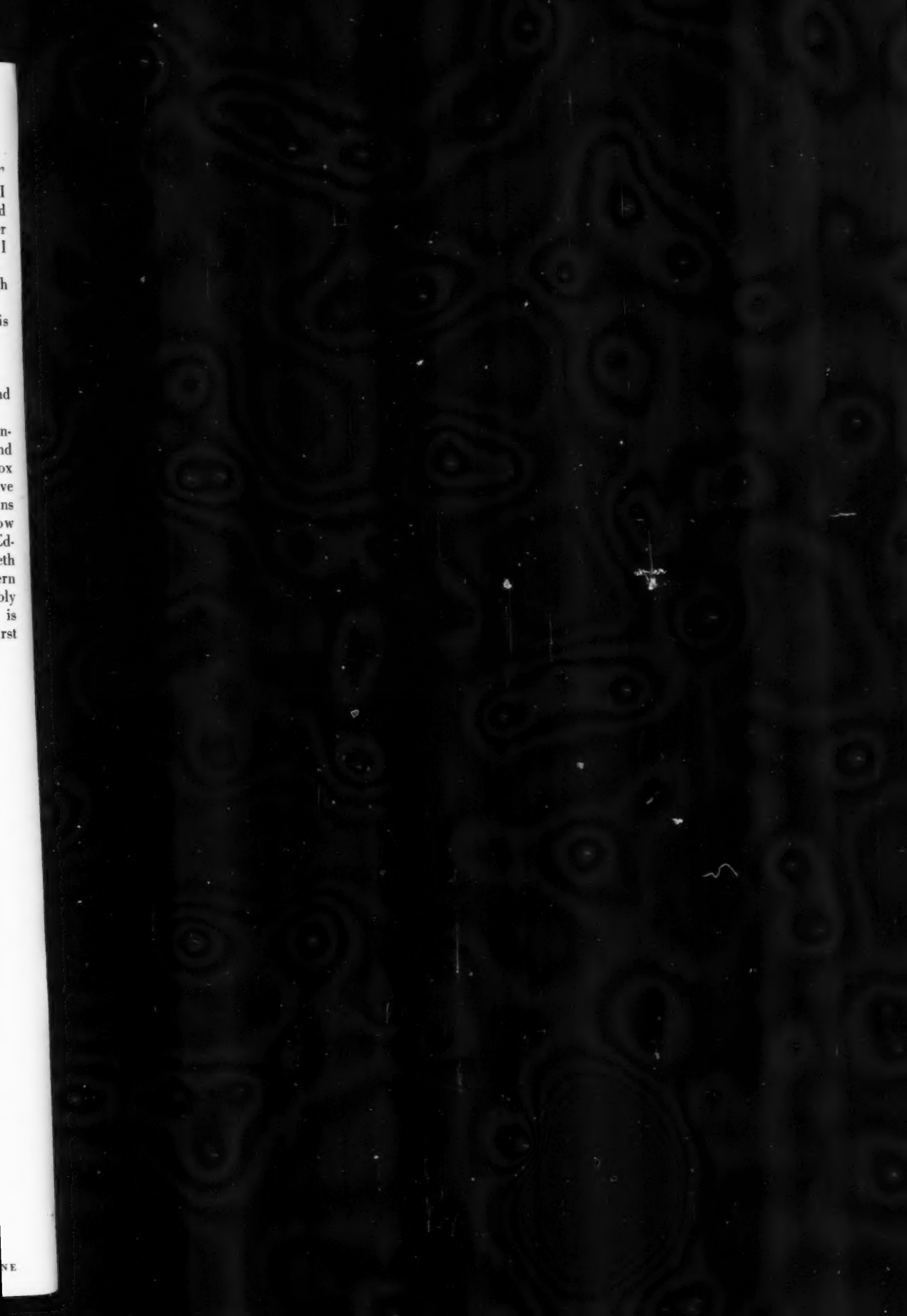
When business is terribly slow
And nobody seems to be sick,
And everything's dullish, you know,
Here's what you can do, and do quick:

Look out at the office and see
That there's nobody there but the nurse,
And feel yourself utterly free
(A feeling than which there is worse),

Then say in a confident tone
Or think to yourself, if you will,
That you'll leave for the day.—There's the phone,
And the office is starting to fill.

FUNNY STORY

"The operation was successful—
The patient died."
The jokester laughed and laughed and laughed
Until he cried.

He laughed the more because it seemed
So very fitting
To make this quip when all around
Were surgeons sitting.

And when, one day, this jokester breathed
His final breath,
His doctor certified: "He laughed
Himself to death."